Hines
09/857843

-key terms

FILE 'REGISTRY' ENTERED AT 08:57:19 ON 26 OCT 2001
E ADHESIN/CN
L1 239 SEA ABB=ON PLU=ON ADHESIN ?/CN
E HEAT SHOCK PROTEIN/CN
L2 237 SEA ABB=ON PLU=ON HEAT SHOCK PROTEIN ?/CN
E HEAT SHOCK PROTEINS/CN
E HIN47/CN

FILE 'CAPLUS' ENTERED AT 08:58:25 ON 26 OCT 2001
L3 5982 SEA ABB=ON PLU=ON (HEMOPHIL? OR HAEMOPHIL? OR H)(W)INFLUENZ?
L4 667 SEA ABB=ON PLU=ON L3 AND ANTIGEN
L5 38 SEA ABB=ON PLU=ON L4 AND (L1 OR ADHESIN OR HMW# OR (HIGH OR HI)(W)(MOL OR MOLECUL?)(W)(WT OR WEIGHT))
L6 4 SEA ABB=ON PLU=ON L5 AND (L2 OR HEAT SHOCK PROTEIN OR HSP OR HIN47 OR HIN 47)

L6 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:101328 CAPLUS
DOCUMENT NUMBER: 134:146387
TITLE: Immuno-protective and non-toxic Gram-neg. bleb vaccine suitable for pediatric use
INVENTOR(S): Berthet, Francois-xavier Jacques; Dalemans, Wilfried L. J.; Denoel, Philippe; Dequesne, Guy; Feron, Christiane; Lobet, Yves; Poolman, Jan; Thiry, Georges; Thonnard, Joelle; Voet, Pierre
PATENT ASSIGNEE(S): Smithkline Beecham Biologicals S.A., Belg.
SOURCE: PCT Int. Appl., 128 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001009350	A2	20010208	WO 2000-EP7424	20000731
WO 2001009350	A3	20010830		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: GB 1999-18319 A 19990803

AB The present invention relates to an immuno-protective and non-toxic Gram-neg. bleb vaccine suitable for pediatric use. Examples of the Gram-neg. strains from which the blebs are made are N. meningitidis, M. catarrhalis and **H. influenzae**. The blebs of the invention are improved by one or more genetic changes to the chromosome of the bacterium, including up-regulation of protective **antigens**, down-regulation of immunodominant non-protective **antigens**, and detoxification of the Lipid A moiety of LPS.

L6 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:63846 CAPLUS
DOCUMENT NUMBER: 134:120915
TITLE: Multicomponent vaccine to protect against disease caused by **Haemophilus influenzae** and Moraxella catarrhalis
INVENTOR(S): Loosmore, Sheena M.; Yang, Yan-Ping; Klein, Michel H.; Sasaki, Ken
PATENT ASSIGNEE(S): Connaught Laboratories Limited, Can.
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005424	A2	20010125	WO 2000-CA811	20000711
WO 2001005424	A3	20010802		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-353617 A 19990715

AB A multi-valent immunogenic compn. confers protection on an immunized host against infection caused by both **Haemophilus influenzae** and Moraxella catarrhalis. Such compn. comprises at least four **antigens** comprising at least one **antigen** from **Haemophilus influenzae**, and at least one **antigen** from Moraxella catarrhalis. Three of the **antigens** are **adhesins**. **High mol. wt.** (**HMW**) proteins and **Haemophilus influenzae adhesin** (Hia) proteins of non-typeable Haemophilus and a 200 kDa outer membrane protein of Moraxella catarrhalis comprise the **adhesin** components while the other **antigen** is a non-proteolytic analog of **Hin47** protein. Each component does not impair the immunogenicity of the others. The multi-valent immunogenic compn. may be combined with DTP component vaccines, which may also include non-virulent poliovirus and PRP-T, to provide a component vaccine without impairment of the immunogenic properties of the other **antigens**.

L6 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:628017 CAPLUS
DOCUMENT NUMBER: 133:221585
TITLE: Multi-component vaccine against non-typeable **Haemophilus influenzae**
INVENTOR(S): Loosmore, Sheena M.; Yang, Yan-Ping; Klein, Michel H.
PATENT ASSIGNEE(S): Connaught Laboratories Limited, Can.

SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000051633	A2	20000908	WO 2000-CA207	20000229
WO 2000051633	A3	20010125		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-261182 A 19990303

AB The authors disclose a vaccine compn. comprising at least three different **antigens** of **Haemophilus influenzae**, two of which are **adhesins**. **High mol. wt.** (**HMW**) proteins and **Haemophilus influenzae adhesin** (Hia) proteins comprise the **adhesin** components while the other **antigen** is a non-proteolytic analog of **Hin47** protein. Each component does not impair the immunogenicity of the others. The multi-component vaccine afforded protection against otitis media in a chinchilla nasopharyngeal colonization model and partial protection in intrabulla challenge. The Haemophilus vaccine may be combined with DTP vaccine components to provide a multi-valent vaccine without impairment of the immunogenic properties of the other **antigens**.

L6 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:420981 CAPLUS
DOCUMENT NUMBER: 133:57570
TITLE: Multi-component vaccine comprising at least two **antigens** from **Haemophilus influenzae** to protect against disease
INVENTOR(S): Loosmore, Sheena M.; Yang, Yan-ping; Klein, Michel H.
PATENT ASSIGNEE(S): Connaught Laboratories Ltd., Can.
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000035477	A2	20000622	WO 1999-CA1189	19991215
WO 2000035477	A3	20001026		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU,

ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1140158 A2 20011010 EP 1999-957822 19991215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,
PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.: US 1998-210995 A 19981215
WO 1999-CA1189 W 19991215

AB A multi-component immunogenic compn. confers protection on an immunized host against infection caused by **Haemophilus influenzae** . Such compn. comprises at least two different **antigens** of **Haemophilus influenzae** , one of which is an **adhesin**. **High mol. wt.** (**HMW**) proteins of non-typeable **Haemophilus influenzae** enhance the immune response in a host to a non-proteolytic analog of **Hin47** protein in such immunogenic compns. with one component not impairing the immunogenicity of the other. The Haemophilus vaccine may be combined with DTP component vaccines to provide a multi-valent component vaccine without impairment of the immunogenic properties of the other **antigens**.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 09:03:33 ON 26 OCT 2001)
L7 4 S L6
L8 4 DUP REM L7 (0 DUPLICATES REMOVED)

L8 ANSWER 1 OF 4 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-138654 [14] WPIDS
DOC. NO. CPI: C2001-041027
TITLE: New isolated polynucleotide useful for outer membrane vesicle preparation from Gram-negative bacterial strain for vaccination of microbial infections.
DERWENT CLASS: B04 D16
INVENTOR(S): BERTHET, F J; DALEMANS, W L J; DENOEL, P; DEQUESNE, G; FERON, C; LOBET, Y; POOLMAN, J; THIRY, G; THONNARD, J; VOET, P
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM BIOLOGICALS
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001009350	A2	20010208	(200114)*	EN	127

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000068336 A 20010219 (200129)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001009350 A2		WO 2000-EP7424	20000731
AU 2000068336 A		AU 2000-68336	20000731

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000068336 A	Based on	WO 200109350

PRIORITY APPLN. INFO: GB 1999-18319 19990803
AN 2001-138654 [14] WPIDS
AB WO 200109350 A UPAB: 20010312
NOVELTY - An isolated polynucleotide sequence which hybridizes under highly stringent conditions to at least a 30 nucleotide portion of 80 sequences described in the specification.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:

(1) a genetically-engineered outer membrane vesicle (bleb) preparation from a Gram-negative bacterial strain characterized in that the preparation is obtainable by employing a process comprising:

(a) introducing a heterologous gene, optionally controlled by a strong promoter sequence, into the chromosome by homologous recombination; and

(b) making blebs from the strain;

(2) a vaccine comprising a bleb preparation and a pharmaceutically acceptable excipient;

(3) a vector suitable for performing recombination events;

(4) a modified Gram-negative bacterial strain from which the bleb preparation is made;

(5) an immuno-protective and non-toxic Gram-negative bleb, ghost, or killed whole cell vaccine suitable for paediatric use.

ACTIVITY - Antiviral; Antibacterial; Antifungal.

Animals were immunized three times with 5 micro g of the different OMVs absorbed on Al(OH)3 on days 0, 14, and 28. Bleedings were done on days 28 and 35, and they were challenged on day 35. The challenge dose was 20 X LD50 (approx. 10 to the power of 7 CFU/mouse). Mortality rate was monitored for 7 days after challenge.

OMVs injected were:
Group1: Cps-, PorA+
Group2: Cps-, PorA-
Group3: Cps-, PorA-, NspA+
Group4: Cps-, PorA-, Omp85+
Group5: Cps-, PorA-, Hsf+

24 hours after the challenge, there was 100% mortality in the negative control group, while mice immunized with the 5 different OMVs preparations were still alive. Sickness was also monitored during the 7 days and the mice immunized with the NSPA over-expressed blebs appeared to be less sick than the other groups. PorA present in PorA+ blebs is likely to confer extensive protection against infection by the homologous strain. However, protection induced by PorA-up-regulated blebs is likely to be due at least to some extent, to the presence of increased amount of NspA, OMP85 or Hsf.

MECHANISM OF ACTION - Vaccine.

USE - The claimed polynucleotide sequence is used in performing a homologous recombination event within 1000 base pairs upstream of a Gram-negative bacterial chromosomal gene in order to either increase or decrease expression of the gene. The bleb preparation is useful in the manufacture of a medicament for immunizing a human host against a disease caused by infection of one or more of the following: Neisseria meningitidis, Neisseria gonorrhoeae, **Haemophilus influenza**, Moraxella catarrhalis, Pseudomonas aeruginosa, Chlamydia trachomatis, and Chlamydia pneumonia. The invention is useful for immunizing a human host against the diseases caused by the above. The invention also provides immunization against the influenza virus. Immuno-protective and non-toxic Gram-negative bleb, ghost, or killed whole cell vaccines are useful for paediatric use (all claimed).

ADVANTAGE - The vaccine is more immunogenic, less toxic, and safer.

Dwg.0/17

L8 ANSWER 2 OF 4 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2000-594140 [56] WPIDS
DOC. NO. CPI: C2000-177374
TITLE: Vaccine comprising 3 different **antigens** of **Haemophilus influenzae**, 2 of which are **adhesins**, useful for protection against diseases caused by **Haemophilus influenza**, especially otitis media.
DERWENT CLASS: B04 D16
INVENTOR(S): KLEIN, M H; LOOSMORE, S M; YANG, Y
PATENT ASSIGNEE(S): (CONN-N) CONNAUGHT LAB LTD
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000051633	A2	20000908	(200056)*	EN	49

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000027904 A 20000921 (200065)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000051633	A2	WO 2000-CA207	20000229
AU 2000027904	A	AU 2000-27904	20000229

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000027904	A	Based on	WO 200051633

PRIORITY APPLN. INFO: US 1999-261182 19990303
AN 2000-594140 [56] WPIDS
AB WO 200051633 A UPAB: 20001106
NOVELTY - An immunogenic composition for conferring protection in a host against a disease caused by **Haemophilus influenzae** comprising at least 3 different **antigens** of **H. influenzae**, at least 2 of which are **adhesins**, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method of immunizing a host against a disease caused by infection with **H. influenzae** including otitis media, by administering the composition.

ACTIVITY - Auditory. Fifty micro g each of rHMW, rHia and H91A **hin47** were mixed and chinchillas were immunized intramuscularly on days 0, 14, and 28 with 25, 50 or 100 micro g of the mixture. On day 44, chinchillas were challenged with 108 colony forming units (cfu) of live bacteria delivered intranasally (50 micro l per nares). Results indicated that there was excellent protection afforded in the nasopharyngeal colonization challenge model by the 3-component vaccine.

MECHANISM OF ACTION - Vaccine.

USE - The multivalent vaccine is useful as protection against encapsulated and non-encapsulated **H. influenzae** diseases, such as otitis media.

Dwg.0/22

L8 ANSWER 3 OF 4 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-431500 [37] WPIDS
DOC. NO. CPI: C2000-131168
TITLE: New immunogenic composition for conferring protection in a host against a disease caused by **Haemophilus influenzae**, comprises two different **antigens** of **H. influenzae**, where one of the **antigens** is an **adhesin**.
DERWENT CLASS: B04 D16
INVENTOR(S): KLEIN, M H; LOOSMORE, S M; YANG, Y
PATENT ASSIGNEE(S): (CONN-N) CONNAUGHT LAB LTD; (KLEI-I) KLEIN M H; (LOOS-I) LOOSMORE S M; (YANG-I) YANG Y
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000035477	A2	20000622	(200037)*	EN	44
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000015439	A	20000703	(200046)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000035477	A2	WO 1999-CA1189	19991215

AU 2000015439 A AU 2000-15439 19991215

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2000015439 A	Based on	WO 200035477

PRIORITY APPLN. INFO: US 1998-210995 19981215
AN 2000-431500 [37] WPIDS
AB WO 200035477 A UPAB: 20000807
NOVELTY - A new immunogenic composition (I) for conferring protection in a host against a disease caused by **Haemophilus influenzae**, comprises at least two different **antigens** of **Haemophilus influenzae**, where at least one of the **antigens** is an **adhesin**.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a method of immunizing a host against disease caused by infection with **Haemophilus influenzae**, including otitis media, comprising administering to the host an immunoeffective amount of (I).

ACTIVITY - Antibacterial.

MECHANISM OF ACTION - Vaccine.

H91A **Hin47** is partially protective in the chinchilla model of otitis media, as described in the US Patent No. 5,506,139.

In this model, 1 to 2 year old chinchillas (Moulton Chinchilla Ranch, Rochester, Minnesota) were immunized intramuscularly (i.m.) on days 0, 14 and 28 with 30 micro g of H91A **Hin47** adsorbed to alum, and challenged on day 44 with 50 to 350 colony forming units (cfu) of live organisms delivered into the middle ear space via the epitympanic bulla. Animals were monitored by tympanometry and middle ear fluid was collected 4 days post challenge, mixed with 200 micro l of BHI (undefined) medium and dilutions plated onto chocolate agar plates that were incubated for 24 hours at 37 deg. C. Convalescent animals or those mock-immunized with alum alone, were used as controls. For the multi-component vaccine study, 50 micro g of H91A **Hin47** was mixed with 50 micro g of recombinant **HMW** (rHMW) and chinchillas were immunized as described above.

The results of the protection study indicate that there was still partial protection afforded in the intrabulla challenge model by the combination of H91A **Hin47** and rHMW.

USE - The two different **antigens** of **H. influenzae**, at least one of which is an **adhesin**, are useful in the manufacture of a vaccine for conferring protection against disease caused by infection with **H. influenzae**, including otitis media. (I) is used as a vaccine (all claimed) against diseases caused by **H. influenzae** infection.

Dwg.0/12

L8 ANSWER 4 OF 4 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 97136564 EMBASE
DOCUMENT NUMBER: 1997136564
TITLE: Brief heat shock treatment induces a long-lasting alteration in the glycolipid receptor binding specificity and growth rate of **Haemophilus**

influenzae.

AUTHOR: Hartmann E.; Lingwood C.
CORPORATE SOURCE: C. Lingwood, Department of Microbiology, Research Institute, Hospital for Sick Children, Toronto, Ont., Canada. cling@sickkids.on.ca
SOURCE: Infection and Immunity, (1997) 65/5 (1729-1733).
Refs: 38
ISSN: 0019-9567 CODEN: INFIBR
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English
AB After brief heat shock treatment, clinical strains of nontypeahle **Haemophilus influenzae** show a long-lasting change in the binding specificity for glycolipids and a markedly increased growth rate in vitro. Non- heatshocked **H. influenzae** specifically binds to phosphatidylethanolamine (PE), gangliotetraosylceramide (Gg4), and gangliotriosylceramide (Gg3) and binds minimally to sulfatoxygalactosylceramide (SGC; also called sulfatide). After a 5-min heat shock at 42.degree.C, strains of **H. influenzae** showed a marked increase in binding to SGC and acquired the ability to bind to sulfatoxygalactosylglycerol (SGG) in thin-layer chromatography overlays. Additionally, heat-shocked **H. influenzae** cells showed an increased growth rate (twofold). Increased sulfatide binding and growth rate were retained for approximately 60 generations, after which the heat-shocked organisms reverted to their original glycolipid binding pattern (i.e., PE, Gg3, and Gg4) and growth rate. Such organisms could then be reexposed to heat, and the heat shock phenotype would be reestablished. After exposure of the organisms to brief heat shock, Western blotting of a surface extract of **H. influenzae** with anti-bovine-brain **hsp**-70 monoclonal antibody showed an increase in two protein bands at 82 and 60 kDa. This antibody was a potent inhibitor of the binding of heat-shocked **H. influenzae** to SGC and SGG but had no effect on PE, Gg3, or Gg4 binding in vitro. In contrast, an antibody against an **H. influenzae** PE-Gg3-Gg4-binding **adhesin** that was recently identified (J. Busse, E. Hartmann, and C. A. Lingwood, J. Infect. Dis. 175:77-83, 1996) selectively inhibited the organism's binding to PE and Gg3. This indicates that cell surface **hsp**-70-related **heat shock proteins** can mediate **H. influenzae** attachment to sulfoglycolipids following heat shock. We suggest that such increased binding to sulfated glycolipids may be a response to fever following **H. influenzae** infection in humans.

FILE 'MEDLINE' ENTERED AT 09:07:10 ON 26 OCT 2001
E HEMOPHILUS INFLUENZAE/CT
E HAEMOPHILUS INFLUENZAE/CT
L9 8242 S E3
E ANTIGENS/CT
L10 47446 S E3
L11 28 S L9 AND L10

L11 ANSWER 1 OF 28 MEDLINE
AN 2000231785 MEDLINE

TI Identification of a Haemophilus influenzae 5'-nucleotidase protein: cloning of the nucA gene and immunogenicity and characterization of the NucA protein.
AU Zagursky R J; Ooi P; Jones K F; Fiske M J; Smith R P; Green B A
SO INFECTION AND IMMUNITY, (2000 May) 68 (5) 2525-34.
Journal code: GO7; 0246127. ISSN: 0019-9567.
AB We report on the identification of a surface-exposed, highly conserved, immunogenic nontypeable Haemophilus influenzae (NTHi) protein, which elicits cross-reactive bactericidal antibodies against NTHi. The protein was extracted from NTHi strain P860295 with KSCN and purified; it migrated as a single band on a sodium dodecyl sulfate-polyacrylamide gel with an apparent molecular mass of 63 kDa. Mouse antiserum generated against the purified protein was reactive on whole-cell enzyme-linked immunosorbent assay (ELISA) with seven NTHi strains and type b Eagan and Whittier strains and exhibited bactericidal activity to homologous and heterologous NTHi strains. However, the protein is made in small amounts in NTHi as corroborated by immunoelectron microscopy. To further study this protein, we cloned, sequenced, and expressed it recombinantly in Escherichia coli. The recombinant protein is localized in the periplasm of E. coli and has been purified to homogeneity. Both the recombinant and native proteins possess 5'-nucleotidase activity; hence, the protein has been called NucA. Mouse antiserum directed against the recombinant NucA protein was reactive on Western immunoblots and whole-cell ELISA with all H. influenzae strains tested including Eagan and was bactericidal for two heterologous strains tested. The antiserum also resulted in a log reduction in bacteremia, in an infant-rat protection study with H. influenzae type b as the challenge strain. These features suggest that NucA is a potential subunit vaccine candidate against NTHi disease.

L11 ANSWER 2 OF 28 MEDLINE
AN 94221158 MEDLINE
TI Effector functions of IgG subclass antibodies.
AU Bredius R G; Van de Winkel J G; Weening R S; Out T A
SO IMMUNODEFICIENCY, (1993) 4 (1-4) 51-3.
Journal code: BSP; 9418574. ISSN: 1067-795X.

L11 ANSWER 3 OF 28 MEDLINE
AN 91034199 MEDLINE
TI Combined inheritance of epithelial and erythrocyte receptors for Haemophilus influenzae.
AU van Alphen L; Levene C; Geelen-van den Broek L; Poole J; Bennett M; Dankert J
SO INFECTION AND IMMUNITY, (1990 Nov) 58 (11) 3807-9.
Journal code: GO7; 0246127. ISSN: 0019-9567.
AB Haemophilus influenzae type b expressing fimbriae showed no adherence to buccal epithelial cells and no agglutination of erythrocytes from three AnWj-negative siblings in one family. Hemagglutination of erythrocytes from 13 AnWj-positive members of the same family and from 24 controls was normal, and H. influenzae adhered well to buccal epithelial cells from them. These data indicate that the expression of epithelial and erythrocyte receptors for H. influenzae is inherited concomitantly. Combined with previous data (L. van Alphen, J. Poole, L. Geelen, and H. Zanen, Infect. Immun. 55:2355-2358, 1987), the results show that the receptor molecules on the surfaces of the epithelial cell and the erythrocyte are different but that the binding sites for the fimbriae of H.

influenzae are similar.

L11 ANSWER 4 OF 28 MEDLINE
AN 87229872 MEDLINE
TI Chemical perspectives in the design of a pediatric meningitis vaccine.
AU Penney C L
SO NEW YORK STATE JOURNAL OF MEDICINE, (1987 Apr) 87 (4) 226-9. Ref: 33
Journal code: OBA; 0401064. ISSN: 0028-7628.

L11 ANSWER 5 OF 28 MEDLINE
AN 80016765 MEDLINE
TI Lymphocytes from adenoid vegetations: proliferative responses in vitro as compared to blood lymphocytes.
AU Mogensen H H; Meistrup-Larsen K I; Andersen V
SO ACTA PATHOLOGICA ET MICROBIOLOGICA SCANDINAVICA. SECTION C, IMMUNOLOGY, (1979 Jun) 87C (3) 197-202.
Journal code: 103; 7508469. ISSN: 0304-1328.
AB Thymidine incorporation by lymphocytes obtained from adenoids (AVL) and blood (PBL) were compared in 27 children undergoing adenoidectomy. Optimal conditions as regards cell number and duration of culture were worked out. The spontaneous thymidine incorporation was higher in PBL than in AVL. In cultures stimulated by polyclonal activators or by PPD, the responses of PBL were higher. The dose-response curves for PBL and AVL after stimulation with killed H. influenzae were different: PBL showed a higher response, the optimal antigen concentration was lower for PBL, and the responsiveness to suboptimal antigen concentrations wash higher in PBL than in AVL.

L11 ANSWER 6 OF 28 MEDLINE
AN 77165680 MEDLINE
TI Counterimmunoelectrophoresis in the diagnosis of bacterial meningitis.
AU Colding H; Lind I
SO JOURNAL OF CLINICAL MICROBIOLOGY, (1977 Apr) 5 (4) 405-9.
Journal code: HSH; 7505564. ISSN: 0095-1137.
AB The aim of the present study was to investigate whether counterimmunoelectrophoresis (CIE) would facilitate the rapid, etiological diagnosis of bacterial meningitis when used in parallel with other routine methods in a medical bacteriological laboratory. Of 3,674 consecutive specimens of cerebrospinal fluid (CSF) received at the Department of Diagnostic Bacteriology, Statens Seruminstitu, 283 specimens (each representing one patient) were selected for examination by CIE on the basis of the following criteria: bacteria or pleocytosis or both by microscopy or positive culture or both. CIE was performed with antisera to Neisseria meningitidis (groups A, B and C), Streptococcus pneumoniae (omni-serum and pools A to 1), and Haemophilus influenzae type b. Antigen was detected in 57% (72/126) of specimens in which cultures revealed these three kinds of microorganisms in CSF and in 12% (17/139) of the culture-negative specimens. CSF specimens from 21 patients with bacterial meningitis caused by other species were all negative in CIE, except four, three of which contained Escherichia coli antigen reacting with antiserum to N. meningitidis group B and one E. coli antigen reacting with antiserum to H. influenzae type b. Specific diagnosis was achieved in 60% (170/283) of the specimens studied and could be extablished

within 1 h in 85% (145/170) by the combined results of microscopy and CIE. Ten specimens, nine of which showed a reaction with antiserum to N. meningitidis group A, were positive by CIE only.

L11 ANSWER 7 OF 28 MEDLINE
AN 76015604 MEDLINE
TI [Studies on the specificity of antisera against denaturated desoxyribonucleic acids].
Untersuchungen zur Spezifitat von Antiseren gegen denaturierte Desoxyribonukleinsauren.
AU Storl H J; Simon H; Barthelmes H
SO ACTA BIOLOGICA ET MEDICA GERMANICA, (1974) 33 (4) 485-95.
Journal code: 0E6; 0370276. ISSN: 0001-5318.

L11 ANSWER 8 OF 28 MEDLINE
AN 75163201 MEDLINE
TI Natural history of otitis media.
AU Howie V M
SO ANNALS OF OTOLOGY, RHINOLOGY AND LARYNGOLOGY, (1975 Mar-Apr) 84 (2 PT2 SUPPL 19) 67-72.
Journal code: 5Q2; 0407300. ISSN: 0003-4894.

L11 ANSWER 9 OF 28 MEDLINE
AN 75010596 MEDLINE
TI Hemophilus influenzae b meningitis in identical twins of a triplet sibship.
AU Coulter D; Whisnant J K; Marks M I
SO PEDIATRICS, (1974 Oct) 54 (4) 502-4.
Journal code: OXV; 0376422. ISSN: 0031-4005.

L11 ANSWER 10 OF 28 MEDLINE
AN 74305388 MEDLINE
TI Partially treated meningitis.
AU Lewin E B
SO AMERICAN JOURNAL OF DISEASES OF CHILDREN, (1974 Aug) 128 (2) 145-7.
Journal code: 3GS; 0370471. ISSN: 0002-922X.

L11 ANSWER 11 OF 28 MEDLINE
AN 73066089 MEDLINE
TI Countercurrent immunoelectrophoresis in the diagnosis of systemic diseases caused by Hemophilus infleunzae type b.
AU Ingram D L; Anderson P; Smith D H
SO JOURNAL OF PEDIATRICS, (1972 Dec) 81 (6) 1156-9.
Journal code: JLZ; 0375410. ISSN: 0022-3476.

L11 ANSWER 12 OF 28 MEDLINE
AN 72207702 MEDLINE
TI Antigen-free medium for cultivation of Haemophilus influenzae, AFH-medium.
AU Branefors-Helander P
SO ACTA PATHOLOGICA ET MICROBIOLOGICA SCANDINAVICA. SECTION B: MICROBIOLOGY AND IMMUNOLOGY, (1972) 80 (2) 211-20.
Journal code: API; 7508470. ISSN: 0365-5571.

L11 ANSWER 13 OF 28 MEDLINE
AN 72201339 MEDLINE
TI An Escherichia coli antigen cross-reactive with the capsular polysaccharide of Haemophilus influenzae type b: occurrence among

known serotypes, and immunochemical and biologic properties of E. coli antisera toward H. influenzae type b.
AU Schneerson R; Bradshaw M; Whisnant J K; Myerowitz R L; Parke J C Jr; Robbins J B
SO JOURNAL OF IMMUNOLOGY, (1972 Jun) 108 (6) 1551-62.
Journal code: IFB; 2985117R. ISSN: 0022-1767.

L11 ANSWER 14 OF 28 MEDLINE
AN 72077016 MEDLINE
TI Bacterial and dietary antibodies in liver disease.
AU Triger D R; Alp M H; Wright R
SO LANCET, (1972 Jan 8) 1 (7741) 60-3.
Journal code: L0S; 2985213R. ISSN: 0140-6736.

L11 ANSWER 15 OF 28 MEDLINE
AN 72042824 MEDLINE
TI Lymphocyte transformation with bacterial antigens in intrinsic asthma.
AU Virtue C M; Wittig H J; Cook T J
SO JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY, (1971 Dec) 48 (6) 321-30.
Journal code: H53; 1275002. ISSN: 0091-6749.

L11 ANSWER 16 OF 28 MEDLINE
AN 72021219 MEDLINE
TI Serotyping of noncapsular Haemophilus influenzae.
AU Kirkman J B Jr; Crawford J J
SO APPLIED MICROBIOLOGY, (1971 Jul) 22 (1) 133-4.
Journal code: 6K0; 7605802. ISSN: 0003-6919.

L11 ANSWER 17 OF 28 MEDLINE
AN 72015310 MEDLINE
TI Haemophilus disease and cell-surface antigens.
AU Anonymous
SO LANCET, (1971 Oct 23) 2 (7730) 914.
Journal code: L0S; 2985213R. ISSN: 0140-6736.

L11 ANSWER 18 OF 28 MEDLINE
AN 71203339 MEDLINE
TI [Haemophilus influenzae].
Haemophilus influenzae.
AU Dragomirescu T
SO MICROBIOLOGIA, PARAZITOLOGIA, EPIDEMIOLOGIA, (1971 Mar-Apr) 16 (2) 109-19. Ref: 37
Journal code: MXQ; 0420151. ISSN: 0026-2609.

L11 ANSWER 19 OF 28 MEDLINE
AN 71189928 MEDLINE
TI Bacterial antigens cross-reactive with the capsular polysaccharide of Haemophilus influenzae type b.
AU Bradshaw M W; Schneerson R; Parke J C Jr; Robbins J B
SO LANCET, (1971 May 29) 1 (7709) 1095-6.
Journal code: L0S; 2985213R. ISSN: 0140-6736.

L11 ANSWER 20 OF 28 MEDLINE
AN 71138525 MEDLINE
TI Immunity to Haemophilus influenzae type B: the role of the capsular antibody.

AU Mpairwe Y
SO JOURNAL OF MEDICAL MICROBIOLOGY, (1971 Feb) 4 (1) 85-8.
Journal code: J2N; 0224131. ISSN: 0022-2615.

L11 ANSWER 21 OF 28 MEDLINE
AN 70154422 MEDLINE
TI [Obtainment of type-specific immune serums against Haemophilus influenzae and their suitability for immunofluorescence]. Gewinnung typenspezifischer Immunseren gegen Haemophilus influenzae und ihre Eignung fur die Immunfluoreszenz.
AU Gartner L; Budde E
SO ARCHIV FUR HYGIENE UND BAKTERIOLOGIE, (1969 Jun) 153 (3) 264-9.
Journal code: 78G; 0331541. ISSN: 0003-9144.

L11 ANSWER 22 OF 28 MEDLINE
AN 70083922 MEDLINE
TI Antibody responses to bacterial antigens during exacerbations of chronic bronchitis.
AU Reichek N; Lewin E B; Rhoden D L; Weaver R R; Crutcher J C
SO AMERICAN REVIEW OF RESPIRATORY DISEASE, (1970 Feb) 101 (2) 238-44.
Journal code: 426; 0370523. ISSN: 0003-0805.

L11 ANSWER 23 OF 28 MEDLINE
AN 69232065 MEDLINE
TI Delayed multiplication of newly capsulated transformants of Haemophilus influenzae detected by immunofluorescence.
AU Catlin B W; Tartagni V R
SO JOURNAL OF GENERAL MICROBIOLOGY, (1969 Jun) 56 (3) 387-401.
Journal code: I87; 0375371. ISSN: 0022-1287.

L11 ANSWER 24 OF 28 MEDLINE
AN 68158673 MEDLINE
TI Antigenic relationship of the gram-negative organism causing canine abortion to smooth and rough brucellae.
AU Diaz R; Jones L M; Wilson J B
SO JOURNAL OF BACTERIOLOGY, (1968 Feb) 95 (2) 618-24.
Journal code: HH3; 2985120R. ISSN: 0021-9193.

L11 ANSWER 25 OF 28 MEDLINE
AN 67206241 MEDLINE
TI Antigens of the oral bacterial flora in the dental pulp.
AU Ravnik C; Likar M
SO PATHOLOGIA ET MICROBIOLOGIA, (1967) 30 (2) 208-14.
Journal code: OST; 0401122. ISSN: 0031-2959.

L11 ANSWER 26 OF 28 MEDLINE
AN 66135633 MEDLINE
TI The antigenic structure of Haemophilus and Corynebacterium species from the human genital tract claimed to be associated with or derived from Mycoplasma hominis.
AU Pease P; Laughton N
SO JOURNAL OF GENERAL MICROBIOLOGY, (1965 Dec) 41 (3) 293-7.
Journal code: I87; 0375371. ISSN: 0022-1287.

L11 ANSWER 27 OF 28 MEDLINE
AN 66133055 MEDLINE
TI The antigenic structure of PPLO (Mycoplasma hominis) and related bacteria.

AU Pease P
SO JOURNAL OF GENERAL MICROBIOLOGY, (1965 Dec) 41 (3) 299-308.
Journal code: I87; 0375371. ISSN: 0022-1287.

L11 ANSWER 28 OF 28 MEDLINE
AN 66049899 MEDLINE
TI Relationship between the competence antigen and the competence-activator substance in pneumococci.
AU Tomasz A; Beiser S M
SO JOURNAL OF BACTERIOLOGY, (1965 Nov) 90 (5) 1226-32.
Journal code: HH3; 2985120R. ISSN: 0021-9193.

FILE 'CAPLUS' ENTERED AT 09:15:17 ON 26 OCT 2001
L12 20 S L5 AND (INFECT? OR OTITIS MEDIA)
L13 16 S L12 NOT L6

L13 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:628161 CAPLUS
TITLE: Genetic analysis of virulence factors of Mannheimia (Pasteurella) haemolytica A1
AUTHOR(S): Lo, R. Y. C.
CORPORATE SOURCE: Department of Microbiology, University of Guelph, Guelph, ON, N1G 2W1, Can.
SOURCE: Vet. Microbiol. (2001), 83(1), 23-35
CODEN: VMICDQ; ISSN: 0378-1135
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Using a mol. genetic approach, the genes that code for the various virulence factors of Mannheimia haemolytica A1 have been cloned for detailed characterizations. These included anal. of the encoded proteins, their biol. activities, secretion of the mols. from the bacterium as well as their use in a vaccine component.Two newly characterized **antigens** of M. haemolytica A1 have been identified. The first one is a TonB-dependent iron regulated outer-membrane receptor that is distinct from the transferrin binding proteins. The 84 kDa Irp protein exhibits features including a TonB box and a 50 amino acid region that can adopt occluded .beta.-barrel structures similar to the "plug" domain of the Escherichia coli FhuA and FepA crystal structures. Homologues of Irp were identified by anal. of the genome sequences of a no. of Gram neg. mucosal pathogens, including Neisseria meningitidis and N. gonorrhoeae. The Neisserial irp genes were cloned by PCR and expressed the 84 kDa protein as expected, demonstrating that they are functional genes. In addn. to being regulated by iron and Fur, irpMh undergoes phase variation by a slipped-strand mispairing mechanism and may represent a contingency locus for iron acquisition during an **infection**.Another locus that codes for a putative **adhesin** mol. has also been partially characterized. This putative **adhesin** protein is highly homologous with the **high-mol.-wt.** **adhesin** proteins of non-piliated non-typable strains of **Haemophilus influenzae** (NTHi) including Hia, Hsf, **HMW1, HMW2**. Currently, we have cloned the DNA that codes for 2223 amino acids (225 kDa) and is still missing the stop codon. It is anticipated that when complete, the protein could be close to 240 kDa, similar to the mol. mass of Hsf. Though incomplete, anal. of the **adhesin** showed that it exhibits

characteristics of autotransporter (AT) proteins. The role of this **high-mol.-wt. adhesin** in **infection** is being investigated.

L13 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:688112 CAPLUS
DOCUMENT NUMBER: 133:265639
TITLE: Vaccine
INVENTOR(S): Capiau, Carine; Deschamps, Marguerite; Desmons, Pierre Michel; Laferriere, Craig Antony Joseph; Poolman, Jan; Prieels, Jean-Paul
PATENT ASSIGNEE(S): Smithkline Beecham Biologicals S.A., Belg.
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000056359	A2	20000928	WO 2000-EP2467	20000317
WO 2000056359	A3	20010201		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

GB 1999-6437	A	19990319
GB 1999-9077	A	19990420
GB 1999-9466	A	19990423
GB 1999-16677	A	19990715

AB The present invention relates to the field of bacterial polysaccharide **antigen** vaccines. In particular, the present invention relates to vaccines comprising a pneumococcal polysaccharide **antigen**, typically a pneumococcal polysaccharide conjugate **antigen**, formulated with a protein **antigen** form Streptococcus pneumoniae, and optionally a Th1-inducing adjuvant.

L13 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:282567 CAPLUS
DOCUMENT NUMBER: 133:41851
TITLE: Passive transfer of antiserum specific for immunogens derived from a nontypeable **Haemophilus influenzae** **adhesin** and lipoprotein D prevents **otitis media** after heterologous challenge
AUTHOR(S): Kennedy, Bobbie-Jo; Novotny, Laura A.; Jurcisek, Joseph A.; Lobet, Yves; Bakaletz, Lauren O.
CORPORATE SOURCE: Department of Pediatrics, Division of Molecular Medicine, The Ohio State University College of Medicine and Public Health, Columbus, OH,

43205-2696, USA
SOURCE: Infect. Immun. (2000), 68(5), 2756-2765
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors recently detd. that passive transfer of serum directed against a synthetic peptide called LB1 or a recombinant fusion protein immunogen [LPD-LB1(f)2,1,3] could prevent **otitis media** after challenge with a homologous non-typeable **Haemophilus influenzae** (NTHI) isolate. NTHI residing in the nasopharynx was rapidly cleared from this site, thus preventing it from ascending the eustachian tube and inducing **otitis media** in chinchillas compromised by an ongoing viral upper respiratory tract **infection**. While LB1 is based solely on one NTHI **adhesin**, the latter immunogen, LPD-LB1(f)2,1,3, was designed to incorporate two NTHI **antigens** shown to play a role in the pathogenesis of **otitis media**; lipoprotein D (LPD) and the P5-homologous fimbrin **adhesin**. The design of LPD-LB1(f)2,1,3 also accommodated for the recently demonstrated existence of three major groupings, based on amino acid sequence diversity, in the third surface-exposed region of P5-fimbrin. LPD-LB1(f)2,1,3 was thus designed to potentially confer broader protection against challenge by diverse strains of NTHI. Chinchillas were passively immunized here with serum specific for either LB1 or for LPD-LB1(f)2,1,3 prior to challenge with a member of all three groups of NTHI relative to diversity in region 3. The transferred serum pools were also analyzed for titer, specificity, and several functional activities. The authors found that both serum pools had equiv. ability to mediate C'-dependent killing and to inhibit adherence of NTHI strains to human oropharyngeal cells. When passively transferred, both serum pools significantly inhibited the signs and incidence of **otitis media** induced by any of the three challenge isolates. Despite providing protection against disease, the ability of these antisera to induce total eradication of NTHI from the nasopharynx was not equiv. among NTHI groups. These data thus suggested that while early, complete eradication of NTHI from the nasopharynx was highly protective, redn. of the bacterial load to below a crit. threshold level appeared to be similarly effective.

REFERENCE COUNT: 27
REFERENCE(S):
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(4) Bakaletz, L; Infect Immun 1989, V57, P3226 CAPLUS
(5) Bakaletz, L; Infect Immun 1995, V63, P4188 CAPLUS
(6) Bakaletz, L; Infect Immun 1999, V67, P2746 CAPLUS
(9) Bakaletz, L; Vaccine 1997, V15, P955 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:241525 CAPLUS
DOCUMENT NUMBER: 132:292707
TITLE: **High molecular weight** proteins **HMW1** and

HMW2 as protective **antigens** against non-typable **Haemophilus influenzae infection**

INVENTOR(S): Loosmore, Sheena M.; Yang, Yan-ping; Klein, Michel H.
PATENT ASSIGNEE(S): Connaught Laboratories Limited, Can.
SOURCE: PCT Int. Appl., 307 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000020609	A2	20000413	WO 1999-CA938	19991007
WO 2000020609	A3	20000803		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9960736	A1	20000426	AU 1999-60736	19991007
EP 1117807	A2	20010725	EP 1999-947153	19991007
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1998-167568 A2 19981007
US 1998-206942 A 19981208
WO 1999-CA938 W 19991007

AB **High mol. wt.** (**HMW**) proteins for use as protective **antigens** against **infection** by non-typable **Haemophilus influenzae infection** are manufd. by expression of the cloned genes in Escherichia coli. The proteins are manufd. using a modified **HMW** operon that contains only the portion of the A region that encodes the mature **HMW** protein and the complete B and C regions of the operon. Increased levels of synthesis of the **HMW** proteins can be achieved by including the E. coli cer gene, a further copy of the portion of the A region of the operon encoding the mature protein or both, in the expression vector. Nucleotide and deduced amino acid sequences of the **hmw1** and **hmw2** genes and **HMW1** and **HMW2** proteins, resp., of several non-typeable **Haemophilus influenzae** strain have been identified. The construction of expression vectors, manuf. and purifn. of the proteins and testing of their protective effects in chinchillas are demonstrated.

L13 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:672596 CAPLUS
DOCUMENT NUMBER: 131:281548
TITLE: Methods and compositions for inactivating **infectious** agents using lactoferrin and related molecules
INVENTOR(S): Plaut, Andrew G.; Qiu, Jiazhou

PATENT ASSIGNEE(S): New England Medical Center Hospitals, Inc., USA
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9952545	A1	19991021	WO 1999-US7931	19990412
W: AU, CA, JP				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9935540	A1	19991101	AU 1999-35540	19990412
EP 989860	A1	20000405	EP 1999-917408	19990412
R: AT, BE, CH, DE, DK, FR, GB, LI, LU, NL, SE, IE				

PRIORITY APPLN. INFO.: US 1998-81564 19980413
WO 1999-US7931 19990412

AB A method for substantially reducing the pathogenicity of an **infectious** agent, without killing the **infectious** agent, by removing or degrading a surface protein of the **infectious** agent, by contacting the **infectious** agent with substantially pure, non-pasteurized, naturally occurring lactoferrin under conditions sufficient to remove or degrade the protein, is disclosed.

REFERENCE COUNT: 8
REFERENCE(S):
(1) Legrand; Biochemical Journal 1986, V236, P839 CAPLUS
(2) Nuyens; US 5849885 A 1998 CAPLUS
(3) Qiu; Proceedings of the National Academy of Science USA 1998, V95, P12641 CAPLUS
(4) Stowell; Biochemical Journal 1991, V276, P349 CAPLUS
(5) Tomita; US 5304633 A 1994 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:670087 CAPLUS
DOCUMENT NUMBER: 131:297562
TITLE: Sequence and analysis of LKP pilin structural genes and the LKP pili operon of nontypable **Haemophilus influenzae**
INVENTOR(S): Green, Bruce A.; Brinton, Charles C., Jr.
PATENT ASSIGNEE(S): American Cyanamid Co. and Bactex, Inc., USA
SOURCE: U.S., 48 pp., Cont.-in-part of U. S. 5,643,725.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5968769	A	19991019	US 1995-477326	19950607
US 5643725	A	19970701	US 1994-277231	19940719
WO 9602648	A1	19960201	WO 1995-US8789	19950713
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES,				

FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

CA 2195090	AA	19960201	CA 1995-2195090	19950713
AU 9530972	A1	19960216	AU 1995-30972	19950713
AU 706937	B2	19990701		
EP 771352	A1	19970507	EP 1995-926676	19950713

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE

PRIORITY APPLN. INFO.:
US 1994-277231 19940719
US 1995-473750 19950607
US 1995-477326 19950607
WO 1995-US8789 19950713

AB The structural gene, hipP, for the pilin of serotype 5 non-typable **Haemophilus influenzae** (NTHi) pili and the LKP operon involved in their biosynthesis are cloned and sequenced for use in diagnosis of **infection** and for the development of therapeutics. Probes and primers derived from the gene can be used to detect the bacterium in biol. samples. The invention further relates to a DNA mol. which encodes a pili protein, particularly a tip adhesion protein. The DNA mols. of the invention can be used in a method for assaying a sample, such as a blood sample, for the presence of **Haemophilus influenzae** in the sample. Accordingly, the invention further relates to the use of the DNA mols. as a diagnostic. The invention also relates to a recombinant **Haemophilus influenzae** pili protein, such as a tip adhesion protein. The protein can be employed in a method for immunizing an animal, such as a human, as a therapeutic or diagnostic.

REFERENCE COUNT: 18
REFERENCE(S):
(1) Anon; WO 9319090 1993 CAPLUS
(2) Brinton; US 4801690 1989 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:464181 CAPLUS
DOCUMENT NUMBER: 131:86860
TITLE: Lipooligosaccharide-based vaccine for prevention of Moraxella (Branhamella) catarrhalis **infections** in mammals
INVENTOR(S): Gu, Xin-Xing; Robbins, John B.
PATENT ASSIGNEE(S): The Government of the United States of America, Department of Health and Hum, USA
SOURCE: PCT Int. Appl., 60 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9936086	A1	19990722	WO 1999-US590	19990112
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9922212	A1	19990802	AU 1999-22212	19990112
BR 9906902	A	20001017	BR 1999-6902	19990112
EP 1047447	A1	20001102	EP 1999-902170	19990112
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1998-71483 P 19980113
WO 1999-US590 W 19990112

AB A conjugate vaccine for Moraxella catarrhalis comprising isolated lipooligosaccharide from which esterified fatty acids have been removed, to produce a detoxified lipooligosaccharide (dLOS), or from which lipid A has been removed, to produce a detoxified oligosaccharide (OS), which is linked to an immunogenic carrier. The immunogenic carrier is selected from the group consisting of UspA or CD derived from M. catarrhalis, tetanus toxoid, HMP derived from **Haemophilus influenza**, diphtheria toxoid, detoxified P. aeruginosa toxin A, cholera toxin, pertussis toxin, hepatitis B surface or core **antigen**, rotavirus VP 7 protein, CRM, CRM197, CRM3201 and respiratory syncytial virus F and G protein. The vaccine is useful for preventing **otitis media** and respiratory **infections** caused by M. catarrhalis in mammals, including humans.

REFERENCE COUNT: 7
REFERENCE(S):
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(3) Gu, X; INFECTION AND IMMUNITY 1993, V61(5), P1873 CAPLUS
(4) Gu, X; INFECTION AND IMMUNITY 1996, V64(10), P4047 CAPLUS
(5) Gu, X; INFECTION AND IMMUNITY 1998, V66(5), P1891 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:679987 CAPLUS
DOCUMENT NUMBER: 130:22773
TITLE: Human milk lactoferrin inactivates two putative colonization factors expressed by **Haemophilus influenzae**
AUTHOR(S): Qiu, Jiazhou; Hendrixson, David R.; Baker, Edward N.; Murphy, Timothy F.; St. Geme, Joseph W., III; Plaut, Andrew G.
CORPORATE SOURCE: Department of Medicine, Division of Gastroenterology, Tufts-New England Medical Center, Boston, MA, 02111, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1998), 95(21),

12641-12646
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB **Haemophilus influenzae** is a major cause of **otitis media** and other respiratory tract disease in children. The pathogenesis of disease begins with colonization of the upper respiratory mucosa, a process that involves evasion of local immune mechanisms and adherence to epithelial cells. Several studies have demonstrated that human milk is protective against **H. influenzae** colonization and disease. In the present study, we examd. the effect of human milk on the **H. influenzae** IgA1 protease and Hap **adhesin**, two autotransported proteins that are presumed to facilitate colonization. Our results demonstrated that human milk lactoferrin efficiently extd. the IgA1 protease preprotein from the bacterial outer membrane. In addn., lactoferrin specifically degraded the Hap **adhesin** and abolished Hap-mediated adherence. Extn. of IgA1 protease and degrdn. of Hap were localized to the N-lobe of the bilobed lactoferrin mol. and were inhibited by serine protease inhibitors, suggesting that the lactoferrin N-lobe may contain serine protease activity. Addnl. expts. revealed no effect of lactoferrin on the **H. influenzae** P2, P5, and P6 outer-membrane proteins, which are distinguished from IgA1 protease and Hap by the lack of an N-terminal passenger domain or an extracellular linker region. These results suggest that human milk lactoferrin may attenuate the pathogenic potential of **H. influenzae** by selectively inactivating IgA1 protease and Hap, thereby interfering with colonization. Future studies should examine the therapeutic potential of lactoferrin, perhaps as a supplement in infant formulas.

REFERENCE COUNT: 41
REFERENCE(S):
(1) Anderson, B; J Mol Biol 1989, V209, P711 CAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 9 OF 16 CAPLUS

ACCESSION NUMBER: 1998:296924 CAPLUS
DOCUMENT NUMBER: 129:39889

TITLE: Nasopharyngeal colonization with nontypeable **Haemophilus influenzae** in chinchillas

AUTHOR(S): Yang, Yan-Ping; Loosmore, Sheena M.; Underdown, Brian J.; Klein, Michel H.
CORPORATE SOURCE: Research Center, Pasteur Merieux Connaught Canada, North York, ON, M2R 3T4, Can.

SOURCE: Infect. Immun. (1998), 66(5), 1973-1980
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Colonization of the nasopharynx by a middle ear pathogen is the first step in the development of **otitis media** in humans. The establishment of an animal model of nasopharyngeal colonization would therefore be of great utility in assessing the potential protective ability of candidate vaccine **antigens** (esp. **adhesins**) against **otitis media**. A chinchilla nasopharyngeal colonization model for nontypeable **Haemophilus influenzae** (NTHI) was developed with antibiotic-resistant strains. This model does not require coinfection with a virus. There was no significant difference in the efficiency of NTHI colonization between adult (1- to 2-yr-old) and young (2- to 3-mo-old) animals. However, the incidence of middle ear **infection** following nasopharyngeal colonization was significantly higher in young animals (83 to 89%) than in adult chinchillas (10 to 30%). Chinchillas that had recovered either from a previous middle ear **infection** caused by NTHI or from an **infection** by intranasal inoculation with NTHI were completely protected against nasopharyngeal colonization with a homologous strain and were the best pos. controls in protection studies. Systemic immunization of chinchillas with inactivated whole-cell prepns. significantly protected animals not only against homologous NTHI colonization but also partially against heterologous NTHI **infection**. In all protected animals, significant serum anti-P6 and anti-**HMW** antibody responses were obsd. The outer membrane P6 and **high-mol.-wt**. (**HMW**) proteins appear to be promising candidate vaccine **antigens** to prevent nasopharyngeal colonization and middle ear **infection** caused by NTHI.

L13 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:296912 CAPLUS
DOCUMENT NUMBER: 129:53186
TITLE: Synthesis and characterization of lipooligosaccharide-based conjugates as vaccine candidates for Moraxella (Branhamella) catarrhalis
AUTHOR(S): Gu, Xin-Xing; Chen, Jing; Barenkamp, Stephen J.; Robbins, John B.; Tsai, Chao-Ming; Lim, David J.; Battey, James
CORPORATE SOURCE: Laboratory of Immunology, National Institute on Deafness and Other Communication Disorders, Rockville, MD, 20850, USA
SOURCE: Infect. Immun. (1998), 66(5), 1891-1897
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Moraxella (Branhamella) catarrhalis is an important cause of **otitis media** and sinusitis in children and of lower respiratory tract **infections** in adults. Lipooligosaccharide (LOS) is a major surface **antigen** of the bacterium and elicits bactericidal antibodies. Treatment of the LOS from strain ATCC 25238 with anhyd. hydrazine reduced its toxicity 20,000-fold, as assayed in the Limulus amebocyte lysate (LAL) test. The detoxified LOS (dLOS) was coupled to tetanus toxoid (TT) or **high-mol.-wt.** proteins (HMP)

from nontypeable **Haemophilus influenzae** through a linker of adipic acid dihydrazide to form dLOS-TT or dLOS-HMP. The molar ratios of dLOS to TT and HMP conjugates were 19:1 and 31:1, resp. The antigenicity of the two conjugates was similar to that of the LOS, as detd. by double immunodiffusion. S.c. or i.m. injection of both conjugates elicited a 50- to 100-fold rise in the geometric mean of IgG to the homologous LOS in mice after three injections and a 350- to 700-fold rise of anti-LOS IgG in rabbits after two injections. The immunogenicity of the conjugate was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced antisera had complement-mediated bactericidal activity against the homologous strain and heterologous strains of M. catarrhalis. These results indicate that a detoxified LOS-protein conjugate is a candidate for immunization against M. catarrhalis diseases.

L13 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:425363 CAPLUS
DOCUMENT NUMBER: 127:32828
TITLE: Therapeutic and diagnostic vaccine for the treatment of microbial **infections**
INVENTOR(S): Pascual, David; Bond, Clifford; Burritt, James; Burgess, Don; Glee, Pati; Jutila, John; Jutila, Mark; Bargatze, Robert; Mcfeters, Gordon; Pyle, Barry; Cutler, Jim E.; Han, Yongmoon
PATENT ASSIGNEE(S): Research and Development Institute, Inc., USA; Pascual, David; Bond, Clifford; Burritt, James; Burgess, Don; Glee, Pati; Jutila, John; Jutila, Mark; Bargatze, Robert; et al.
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9718790	A2	19970529	WO 1996-US18796	19961121
WO 9718790	A3	19970731		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2238262	AA	19970529	CA 1996-2238262	19961121
AU 9711226	A1	19970611	AU 1997-11226	19961121
JP 2000503630	T2	20000328	JP 1997-519932	19961121

PRIORITY APPLN. INFO.: US 1995-7477 19951122
WO 1996-US18796 19961121

AB Therapeutic peptides, vaccines and diagnostic agents are disclosed for the treatment of pathogenic **infections**. The agents are capable of binding to mol. address on host cell (e.g. leukocyte, endothelial or epithelial cells, nerve cells), triggering one or more signal transduction pathways and enabling selective pathogen or

toxin to traffic through host tissue. The agents are microbial attachment mols. such as adhesive protein, glycoprotein, lectin, carbohydrate, glycolipid.

L13 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:606388 CAPLUS
DOCUMENT NUMBER: 125:245149
TITLE: Synthesis, characterization, and immunologic properties of detoxified lipooligosaccharide from nontypeable **Haemophilus influenzae** conjugated to proteins
AUTHOR(S): Gu, Xin-Xing; Tsai, Chao-Ming; Ueyama, Tomoyo; Barenkamp, Stephen J.; Robbins, John B.; Lim, David J.
CORPORATE SOURCE: Vaccine Development Unit, Laboratory Cellular Biology, National Institute Deafness Communication Disorders, Rockville, MD, 20850, USA
SOURCE: Infect. Immun. (1996), 64(10), 4047-4053
CODEN: INFIBR; ISSN: 0019-9567
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Nontypeable **Haemophilus influenzae** (NTHi) is an important cause of **otitis media** in children and of pneumonitis in adults with depressed resistance. Lipooligosaccharide (LOS) is a major surface **antigen** of NTHi and elicits bactericidal and opsonic antibodies. We prepd. detoxified LOS (dLOS) protein conjugates from NTHi for use as exptl. vaccines. LOS from NTHi 9274 was treated with anhyd. hydrazine and had its toxicity reduced to clin. acceptable levels. DLOS was bound to tetanus toxoid (TT) or **high-mol.-wt**. proteins (HMPs) from NTHi through a linker of adipic acid dihydrazide to form dLOS-TT or dLOS-HMP. The molar ratio of the dLOS to protein carriers ranged from 26:1 to 50:1. The antigenicity of the conjugates was similar to that of the LOS alone as detd. by double immunodiffusion. S.c. or i.m. injection of the conjugates elicited a 28- to 486-fold rise in the level of IgG antibodies in mice to the homologous LOS after two or three injections and a 169- to 243-fold rise in the level of IgG antibodies in rabbits after two injections. The immunogenicity of the conjugates in mice and rabbits was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced LOS antibodies induced complement-mediated bactericidal activity against the homologous strain 9274 and prototype strain 3189. These results indicate that a detoxified LOS-protein conjugate is a candidate vaccine for **otitis media** and pneumonitis caused by NTHi.

L13 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:455154 CAPLUS
DOCUMENT NUMBER: 125:139983
TITLE: Identification of surface-exposed B-cell epitopes on **high-molecular-weight** adhesion proteins of nontypeable **Haemophilus influenzae**
AUTHOR(S): Barenkamp, Stephen J.; St. Geme, Joseph W., III
CORPORATE SOURCE: Dep. Pediatrics, St. Louis Univ. Sch. Med., St. Louis, MO, 63104-1095, USA

SOURCE: Infect. Immun. (1996), 64(8), 3032-3037
CODEN: INFIBR; ISSN: 0019-9567
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Two surface-exposed **high-mol.-wt.** proteins, **HMW1** and **HMW2**, expressed by a prototypic strain of nontypeable **H. influenzae** (NTHI) mediate attachment to human epithelial cells. These proteins are members of a family of highly immunogenic proteins common to most nontypeable Haemophilus strains. Immunization with an **HMW1-HMW2** mixt. modified the course of disease in an animal model of **otitis media**, suggesting the potential usefulness of these proteins as NTHI vaccine components. Identification of surface-accessible B-cell epitopes could be important to efforts to develop recombinant or synthetic peptide vaccines based upon these **high-mol.-wt** . proteins. The purpose here was to identify surface-accessible epitopes on the **HMW1** and **HMW2** proteins by using monoclonal antibodies (MAbs) and to det. the prevalence of these epitopes among the **high-mol.-wt.** proteins expressed by heterologous nontypeable Haemophilus strains. MAbs were generated by immunizing mice with **high-mol.-wt.** proteins purified from prototype strains and were screened by immunoelectron microscopy (IEM) for the ability to recognize surface epitopes. Two MAbs, designated AD6 and 10C5, that recognized surface epitopes by IEM were recovered. To map the epitopes recognized by these 2 MAbs, a set of **HMW1** and **HMW2** recombinant fusion proteins was constructed using the pGEMEX vectors and the reactivity of the MAbs with these fusion proteins was examd. MAb AD6 recognized an epitope in both **HMW1** and **HMW2** which mapped to the last 75 amino acids at the C termini of the 2 proteins. When examd. for reactivity with heterologous strains, MAb AD6 recognized **high-mol.-wt.** proteins in 75% of 125 unrelated nontypeable Haemophilus strains and, in addn., reacted with 3 of 3 such strains when examd. by IEM. MAb 10C5 recognized an epitope that mapped to a 155-amino-acid segment near the C terminus of **HMW1**. This epitope was adjacent to but distinct from the AD6 epitope and was absent from **HMW2**. The 10C5 epitope was expressed by 40% of the AD6 reactive strains. Identification of shared surface-exposed epitopes on the **high-mol.-wt.** adhesion proteins suggests the possibility of developing recombinant or synthetic peptide-based vaccines protective against disease caused by the majority of NTHI strains.

L13 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1996:190693 CAPLUS
DOCUMENT NUMBER: 124:229356

TITLE: Immunization with **high-molecular-weight** adhesion proteins of nontypeable **Haemophilus influenzae** modifies experimental **otitis media** in chinchillas

AUTHOR(S): Barenkamp, Stephen J.
CORPORATE SOURCE: Department of Pediatrics, Cardinal Glennon Children's Hospital, St. Louis, MO, 63104-1095, USA

SOURCE: Infect. Immun. (1996), 64(4), 1246-51
CODEN: INFIBR; ISSN: 0019-9567
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Prevention of nontypeable **Haemophilus influenzae** **otitis media** by vaccination is an important heath care goal. Proteins important in bacterial adherence deserve consideration as potential vaccine candidates. Two colleagues and I previously identified a family of immunogenic **high-mol.-wt.** proteins important in adherence to nontypeable **H. influenzae** to human epithelial cells (J. W. St. Geme III, S. Falkow, and S. J. Barenkamp, Proc. Natl. Acad. Sci. USA, 90:2875-2879, 1993). In the work described here, I detd. whether immunization with two such adherence proteins, **HMW1** and **HMW2**, purified from prototype nontypeable Haemophilus strain 12, would modify the course of exptl. **otitis media** caused by the homologous strain. Chinchillas received three monthly s.c. injections with 40 .mu.g of a **HMW1/HMW2** protein mixt. in Freund's adjuvant. One month after the last injection, animals were challenged by intrabullar inoculation with 300 CFU of nontypeable **H. influenzae** 12. **Infection** developed in five of five control animals vs. 5 of 10 immunized animals (P = 0.08, Fisher exact, one-tailed). Among **infected** animals, bacterial counts in middle ear fluid specimens 7 days postchallenge were significantly greater in control animals than in immunized animals (P = 0.014, Mann-Whitney U test). Serum antibody titers following immunization were comparable in uninfected and **infected** animals. However, **infection** in immunized animals was uniformly assocd. with the appearance of bacteria downregulated in expression of the **high-mol.-wt.** proteins, suggesting bacterial selection in response to immunol. pressure. Although protection following immunization was incomplete, these data suggest that the **high-mol.-wt.** adhesion proteins are potentially important protective **antigens** which might represent one component of a multicomponent nontypeable Haemophilus vaccine.

L13 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:904941 CAPLUS
DOCUMENT NUMBER: 123:310023
TITLE: The OmpU outer membrane protein, a potential adherence factor of Vibrio cholerae
AUTHOR(S): Sperandio, Vanessa; Giron, Jorge A.; Silveira, Wanderley D.; Kaper, James B.
CORPORATE SOURCE: Center for Vaccine Development, Univ. of Maryland Sch. of Medicine, Baltimore, MD, 21201, USA
SOURCE: Infect. Immun. (1995), 63(11), 4433-8
CODEN: INFIBR; ISSN: 0019-9567
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Expression of the OmpU outer membrane protein of Vibrio cholerae is pos. regulated by toxR, which also regulates crit. virulence factors such as cholera toxin and the toxin-coregulated pilus colonization factor. In this study, we have characterized the 38-kDa OmpU protein and investigated its role in the adhesion of V. **Haemophilus influenzae HMW1** and

HMW2 adhesins, which, in turn, also have similarity with the sequence of Bordetella pertussis filamentous hemagglutinin. A monoclonal antibody directed against FHA recognized both V. cholerae OmpU and Escherichia coli OmpA, and polyclonal anti-OmpU antibodies recognized FHA and E. coli OmpA, suggesting the existence of common epitopes among these proteins. OmpU was strongly recognized by convalescent-phase serum from volunteers exptl. **infected** with virulent V. cholerae strains, indicating that OmpU is immunogenic and produced in vivo. OmpU selectively bound to fibronectin and to an arginine-glycine-asparagine (RGD) tripeptide but not to other matrix glycoproteins tested such as collagen or laminin. Antibodies directed against OmpU or their F(ab)2 fragments completely inhibited adhesion of several V. cholerae strains to HeLa, HEp-2, Caco-2, and Henle 407 epithelial cells and also inhibited intestinal colonization and conferred protection in newborn mice against both bioty8pes (El Tor and classical) of V. cholerae O1. Collectively, these data indicate that OmpU has adhesive properties which may play a role in the pathogenesis of cholera.

L13 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:495780 CAPLUS
DOCUMENT NUMBER: 113:95780
TITLE: Expression in Escherichia coli of a **high-molecular-weight** protective surface **antigen** found in nontypeable and type b **Haemophilus influenzae**
AUTHOR(S): Thomas, W. R.; Callow, M. G.; Dilworth, R. J.; Audesho, A. A.
CORPORATE SOURCE: Clin. Immunol. Res. Unit, Princess Margaret Hosp., Subiaco, 6008, Australia
SOURCE: Infect. Immun. (1990), 58(6), 1909-13
CODEN: INFIBR; ISSN: 0019-9567
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An E. coli clone producing a **high-mol.-wt.** surface **antigen** of **H. influenza** type b (Hib) was isolated from a library of Hib DNA fragments cloned as lysogens in a lambda replacement vector. The **antigen** is found in sarcosyl-insol. outer membrane protein prepns. and was produced by all 36 **H. influenza** isolates tested. Absorption studies indicated that the **antigen** is a surface determinant on all isolates tested. Antibodies to the **antigen** (D15) were found in 8 of 9 convalescent-phase sera from children with invasive Hib **infection**. Affinity-purified antibodies prepd. against the cloned **antigen** gave protection against the development of bacteremia in a rat pup model.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 09:28:41 ON 26 OCT 2001)
L14 79 S L12
L15 75 S L14 NOT L7
L16 44 DUP REM L15 (31 DUPLICATES REMOVED)
L17 28 S L16 AND (VACCIN? OR IMMUNIS? OR IMMUNIZ?)

L17 ANSWER 1 OF 28 MEDLINE

ACCESSION NUMBER: 2001481297 IN-PROCESS
DOCUMENT NUMBER: 21415990 PubMed ID: 11524163
TITLE: Genetic analysis of virulence factors of Mannheimia (Pasteurella) haemolytica A1.
AUTHOR: Lo R Y
CORPORATE SOURCE: Department of Microbiology, University of Guelph, Ont., N1G 2W1, Guelph, Canada.
SOURCE: VETERINARY MICROBIOLOGY, (2001 Oct 22) 83 (1) 23-35. Journal code: XBW; 7705469. ISSN: 0378-1135.
PUB. COUNTRY: Netherlands
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20010830
Last Updated on STN: 20010830

AB Using a molecular genetic approach, the genes that code for the various virulence factors of Mannheimia haemolytica A1 have been cloned for detailed characterizations. These included analysis of the encoded proteins, their biological activities, secretion of the molecules from the bacterium as well as their use in a **vaccine** component.Two newly characterized **antigens** of M. haemolytica A1 have been identified. The first one is a TonB-dependent iron regulated outer-membrane receptor that is distinct from the transferrin binding proteins. The 84kDa Irp protein exhibits features including a TonB box and a 50 amino acid region that can adopt occluded beta-barrel structures similar to the "plug" domain of the Escherichia coli FhuA and FepA crystal structures. Homologues of Irp were identified by analysis of the genome sequences of a number of Gram negative mucosal pathogens, including Neisseria meningitidis and N. gonorrhoeae. The Neisserial irp genes were cloned by PCR and expressed the 84kDa protein as expected, demonstrating that they are functional genes. In addition to being regulated by iron and Fur, irp(Mh) undergoes phase variation by a slipped-strand mispairing mechanism and may represent a contingency locus for iron acquisition during an **infection** .Another locus that codes for a putative **adhesin** molecule has also been partially characterized. This putative **adhesin** protein is highly homologous with the **high-molecular-weight adhesin** proteins of non-piliated non-typable strains of **Haemophilus influenzae** (NTHi) including Hia, Hsf, **HMW1**, **HMW2**. Currently, we have cloned the DNA that codes for 2223 amino acids (225kDa) and is still missing the stop codon. It is anticipated that when complete, the protein could be close to 240kDa, similar to the molecular mass of Hsf. Though incomplete, analysis of the **adhesin** showed that it exhibits characteristics of autotransporter (AT) proteins. The role of this **high-molecular-weight adhesin** in **infection** is being investigated.

L17 ANSWER 2 OF 28 MEDLINE
ACCESSION NUMBER: 2001381130 MEDLINE
DOCUMENT NUMBER: 21108938 PubMed ID: 11163473
TITLE: Developing a nontypeable **Haemophilus influenzae** (NTHi) **vaccine**.
AUTHOR: Poolman J T; Bakaletz L; Cripps A; Denoel P A; Forsgren A; Kyd J; Lobet Y
CORPORATE SOURCE: SmithKline Beecham Biologicals, Rue de l'Institut 89,

1330 Rixensart, Belgium.. jan.poolman@sbbio.be
SOURCE: VACCINE, (2000 Dec 8) 19 Suppl 1 S108-15. Ref: 53
Journal code: X6O; 8406899. ISSN: 0264-410X.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705

AB There is a current high demand for nontypable **Haemophilus influenzae** (NTHi) **vaccines**. Various options for the composition of such **vaccines** are possible. Decisions about the **vaccine** composition have to take into account the antigenic variability of NTHi, so even complex immunogens such as whole bacteria would preferentially have a tailor-made antigenic composition. We will present a summary of NTHi **vaccine** development, describing research efforts from SmithKline Beecham and other laboratories. Currently, major (P1, P2, P4, P5) and minor (P6, D15, TbpA/B, ellipsis) outer membrane proteins, LPS, **adhesins** (**HMW**, Hia, pili, P5) are being studied. Preclinical results with LPD, P5 (LB1) and OMP26 from our laboratories will be described including the use of animal models of otitis and lung **infection**.

L17 ANSWER 3 OF 28 MEDLINE
ACCESSION NUMBER: 2000231815 MEDLINE
DOCUMENT NUMBER: 20231815 PubMed ID: 10768970
TITLE: Passive transfer of antiserum specific for immunogens derived from a nontypeable **Haemophilus influenzae adhesin** and lipoprotein D prevents **otitis media** after heterologous challenge.
AUTHOR: Kennedy B J; Novotny L A; Jurcisek J A; Lobet Y; Bakaletz L O
CORPORATE SOURCE: The Ohio State University College of Medicine and Public Health, Department of Pediatrics, Division of Molecular Medicine, Columbus, Ohio 43205-2696, USA.
CONTRACT NUMBER: DC02830-03 (NIDCD)
SOURCE: INFECTION AND IMMUNITY, (2000 May) 68 (5) 2756-65.
Journal code: GO7; 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000622
Last Updated on STN: 20000622
Entered Medline: 20000613

AB We recently determined that passive transfer of serum directed against a synthetic peptide called LB1 or a recombinant fusion protein immunogen [LPD-LB1(f)(2,1,3)] could prevent **otitis media** after challenge with a homologous nontypeable **Haemophilus influenzae** (NTHI) isolate. NTHI residing in the nasopharynx was rapidly cleared from this site, thus

preventing it from ascending the eustachian tube and inducing **otitis media** in chinchillas compromised by an ongoing viral upper respiratory tract **infection**. While LB1 is based solely on one NTHI **adhesin**, the latter immunogen, LPD-LB1(f)(2,1,3), was designed to incorporate two NTHI **antigens** shown to play a role in the pathogenesis of **otitis media**; lipoprotein D (LPD) and the P5-homologous fimbrin **adhesin**. The design of LPD-LB1(f)(2,1,3) also accommodated for the recently demonstrated existence of three major groupings, based on amino acid sequence diversity, in the third surface-exposed region of P5-fimbrin. LPD-LB1(f)(2,1,3) was thus designed to potentially confer broader protection against challenge by diverse strains of NTHI. Chinchillas were passively **immunized** here with serum specific for either LB1 or for LPD-LB1(f)(2,1,3) prior to challenge with a member of all three groups of NTHI relative to diversity in region 3. The transferred serum pools were also analyzed for titer, specificity, and several functional activities. We found that both serum pools had equivalent ability to mediate C'-dependent killing and to inhibit adherence of NTHI strains to human oropharyngeal cells. When passively transferred, both serum pools significantly inhibited the signs and incidence of **otitis media** ($P \leq 0.01$) induced by any of the three challenge isolates. Despite providing protection against disease, the ability of these antisera to induce total eradication of NTHI from the nasopharynx was not equivalent among NTHI groups. These data thus suggested that while early, complete eradication of NTHI from the nasopharynx was highly protective, reduction of the bacterial load to below a critical threshold level appeared to be similarly effective.

L17 ANSWER 4 OF 28 MEDLINE
ACCESSION NUMBER: 2000211120 MEDLINE
DOCUMENT NUMBER: 20211120 PubMed ID: 10749549
TITLE: **Haemophilus influenzae** in chronic bronchitis.
AUTHOR: Murphy T F
CORPORATE SOURCE: Department of Medicine, State University of New York at Buffalo, NY, USA.
CONTRACT NUMBER: AI19641 (NIAID)
SOURCE: SEMINARS IN RESPIRATORY INFECTIONS, (2000 Mar) 15 (1) 41-51. Ref: 102
Journal code: SEI; 8700961. ISSN: 0882-0546.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000525
Last Updated on STN: 20000525
Entered Medline: 20000518

AB Colonization of the adult respiratory tract with nontypable **Haemophilus influenzae** is a dynamic process with new strains being acquired and replacing old strains periodically.The organism is a common cause of exacerbations of chronic bronchitis based on 3 lines of evidence: quantitative culture of the lower airways obtained by protected specimen brush,

immunoprophylaxis also has potential for preventing OM. Human bacterial polysaccharide immune globulin was protective for pneumococcal OM in children and in the chinchilla OM model. High-dose respiratory syncytial virus-enriched immunoglobulin reduced the incidence and severity of RSV lower respiratory tract **infection** in high-risk children. Passive immunoprophylaxis may also be effective in children with specific immune deficiencies, such as IgG2 deficiency, and patients who fail to respond to **vaccines**.

L17 ANSWER 6 OF 28 MEDLINE
ACCESSION NUMBER: 1998234022 MEDLINE
DOCUMENT NUMBER: 98234022 PubMed ID: 9573078
TITLE: Nasopharyngeal colonization with nontypeable **Haemophilus influenzae** in chinchillas.
AUTHOR: Yang Y P; Loosmore S M; Underdown B J; Klein M H
CORPORATE SOURCE: Research Center, Pasteur Merieux Connaught Canada, North York, Ontario.. ypyang@ca.pmc-vacc.com
SOURCE: INFECTION AND IMMUNITY, (1998 May) 66 (5) 1973-80. Journal code: GO7; 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980520
Last Updated on STN: 19980520
Entered Medline: 19980514

AB Colonization of the nasopharynx by a middle ear pathogen is the first step in the development of **otitis media** in humans. The establishment of an animal model of nasopharyngeal colonization would therefore be of great utility in assessing the potential protective ability of candidate **vaccine antigens** (especially **adhesins**) against **otitis media**. A chinchilla nasopharyngeal colonization model for nontypeable **Haemophilus influenzae** (NTHI) was developed with antibiotic-resistant strains. This model does not require coinfection with a virus. There was no significant difference in the efficiency of NTHI colonization between adult (1- to 2-year-old) and young (2- to 3-month-old) animals. However, the incidence of middle ear **infection** following nasopharyngeal colonization was significantly higher in young animals (83 to 89%) than in adult chinchillas (10 to 30%). Chinchillas that had recovered either from a previous middle ear **infection** caused by NTHI or from an **infection** by intranasal inoculation with NTHI were completely protected against nasopharyngeal colonization with a homologous strain and were found to be the best positive controls in protection studies. Systemic **immunization** of chinchillas with inactivated whole-cell preparations significantly protected animals not only against homologous NTHI colonization but also partially against heterologous NTHI **infection**. In all protected animals, significant serum anti-P6 and anti-**HMW** antibody responses were observed. The outer membrane P6 and **high-molecular -weight** (**HMW**) proteins appear to be promising candidate **vaccine antigens** to prevent nasopharyngeal colonization and middle ear **infection**

caused by NTHI.

L17 ANSWER 7 OF 28 MEDLINE
ACCESSION NUMBER: 1998234010 MEDLINE
DOCUMENT NUMBER: 98234010 PubMed ID: 9573066
TITLE: Synthesis and characterization of lipooligosaccharide-based conjugates as **vaccine** candidates for Moraxella (Branhamella) catarrhalis.
AUTHOR: Gu X X; Chen J; Barenkamp S J; Robbins J B; Tsai C M; Lim D J; Battey J
CORPORATE SOURCE: Laboratory of Immunology, National Institute on Deafness and Other Communication Disorders, Rockville, Maryland 20850, USA..
xgu@pop.nidcd.nih.gov
SOURCE: INFECTION AND IMMUNITY, (1998 May) 66 (5) 1891-7.
Journal code: GO7; 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980520
Last Updated on STN: 19980520
Entered Medline: 19980514

AB Moraxella (Branhamella) catarrhalis is an important cause of **otitis media** and sinusitis in children and of lower respiratory tract **infections** in adults. Lipooligosaccharide (LOS) is a major surface **antigen** of the bacterium and elicits bactericidal antibodies. Treatment of the LOS from strain ATCC 25238 with anhydrous hydrazine reduced its toxicity 20,000-fold, as assayed in the Limulus amebocyte lysate (LAL) test. The detoxified LOS (dLOS) was coupled to tetanus toxoid (TT) or **high-molecular-weight** proteins (HMP) from nontypeable **Haemophilus influenzae** through a linker of adipic acid dihydrazide to form dLOS-TT or dLOS-HMP. The molar ratios of dLOS to TT and HMP conjugates were 19:1 and 31:1, respectively. The antigenicity of the two conjugates was similar to that of the LOS, as determined by double immunodiffusion. Subcutaneous or intramuscular injection of both conjugates elicited a 50- to 100-fold rise in the geometric mean of immunoglobulin G (IgG) to the homologous LOS in mice after three injections and a 350- to 700-fold rise of anti-LOS IgG in rabbits after two injections. The immunogenicity of the conjugate was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced antisera had complement-mediated bactericidal activity against the homologous strain and heterologous strains of M. catarrhalis. These results indicate that a detoxified LOS-protein conjugate is a candidate for **immunization** against M. catarrhalis diseases.

L17 ANSWER 8 OF 28 MEDLINE
ACCESSION NUMBER: 97086309 MEDLINE
DOCUMENT NUMBER: 97086309 PubMed ID: 8932503
TITLE: Progress towards a **vaccine** for nontypable **Haemophilus influenzae.**
AUTHOR: St Geme J W 3rd
CORPORATE SOURCE: Department of Pediatrics, Washington University

School of Medicine, St. Louis, MO, USA.
SOURCE: ANNALS OF MEDICINE, (1996 Feb) 28 (1) 31-7. Ref: 64
Journal code: AMD; 8906388. ISSN: 0785-3890.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 19970414
Last Updated on STN: 19970414
Entered Medline: 19970328

AB Nontypable **Haemophilus influenzae** is a common cause of human disease and is associated with significant morbidity and considerable societal cost. At present, measures to prevent nontypable **H. influenzae** disease are limited to prophylactic antibiotics and, on occasion, exogenous antibody preparations. However, because these interventions are often inadequate, there is interest in developing an effective **vaccine**. Given the marked diversity among epidemiologically unrelated strains and the frequent strain specificity of the immune response to **infection**, efforts have focused on identifying bacterial **antigens** that are highly conserved and capable of stimulating protective antibody. With the recent identification of several such **antigens**, attention must now turn toward selecting the appropriate combination of these molecules and determining the optimal strategy for their presentation to the immune system. The ultimate goal is to induce broad-based and long-lasting protection.

L17 ANSWER 9 OF 28 MEDLINE
ACCESSION NUMBER: 97047678 MEDLINE
DOCUMENT NUMBER: 97047678 PubMed ID: 8926067
TITLE: Synthesis, characterization, and immunologic properties of detoxified lipooligosaccharide from nontypeable **Haemophilus influenzae** conjugated to proteins.
AUTHOR: Gu X X; Tsai C M; Ueyama T; Barenkamp S J; Robbins J B; Lim D J
CORPORATE SOURCE: Vaccine Development Unit, Laboratory of Cellular Biology, National Institute of Deafness and Other Communication Disorders, NIH, Rockville, Maryland 20850, USA.. xgu@pop.nidcd.nih.gov
SOURCE: INFECTION AND IMMUNITY, (1996 Oct) 64 (10) 4047-53.
Journal code: GO7; 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961114

AB Nontypeable **Haemophilus influenzae** (NTHi) is an important cause of **otitis media** in children and of pneumonitis in adults with depressed resistance. Lipooligosaccharide (LOS) is a major surface **antigen** of

NTHi and elicits bactericidal and opsonic antibodies. We prepared detoxified LOS (dLOS) protein conjugates from NTHi for use as experimental **vaccines**. LOS from NTHi 9274 was treated with anhydrous hydrazine and had its toxicity reduced to clinically acceptable levels. dLOS was bound to tetanus toxoid (TT) or **high- molecular-weight** proteins (HMPs) from NTHi through a linker of adipic acid dihydrazide to form dLOS-TT or dLOS-HMP. The molar ratio of the dLOS to protein carriers ranged from 26:1 to 50:1. The antigenicity of the conjugates was similar to that of the LOS alone as determined by double immunodiffusion. Subcutaneous or intramuscular injection of the conjugates elicited a 28- to 486-fold rise in the level of immunoglobulin G antibodies in mice to the homologous LOS after two or three injections and a 169- to 243-fold rise in the level of immunoglobulin G antibodies in rabbits after two injections. The immunogenicity of the conjugates in mice and rabbits was enhanced by formulation with monophosphoryl lipid A plus trehalose dimycolate. In rabbits, conjugate-induced LOS antibodies induced complement-mediated bactericidal activity against the homologous strain 9274 and prototype strain 3189. These results indicate that a detoxified LOS-protein conjugate is a candidate **vaccine** for **otitis media** and pneumonitis caused by NTHi.

L17 ANSWER 10 OF 28 MEDLINE
ACCESSION NUMBER: 96333336 MEDLINE
DOCUMENT NUMBER: 96333336 PubMed ID: 8757830
TITLE: Identification of surface-exposed B-cell epitopes on **high molecular-weight** adhesion proteins of nontypeable **Haemophilus influenzae.**
AUTHOR: Barenkam S J; St Geme J W 3rd
CORPORATE SOURCE: Department of Pediatrics, St. Louis University School of Medicine, Missouri, USA.
CONTRACT NUMBER: AI-21707 (NIAID)
DC-02873 (NIDCD)
SOURCE: INFECTION AND IMMUNITY, (1996 Aug) 64 (8) 3032-7.
Journal code: GO7; 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199609
ENTRY DATE: Entered STN: 19961008
Last Updated on STN: 19961008
Entered Medline: 19960926

AB We previously reported that two surface-exposed **high-molecular-weight** proteins, **HMW1** and **HMW2**, expressed by a prototypic strain of nontypeable **Haemophilus influenzae** (NTHI) mediate attachment to human epithelial cells. These proteins are members of a family of highly immunogenic proteins common to most nontypeable Haemophilus strains. We also reported that **immunization** with an **HMW1-HMW2** mixture modified the course of disease in an animal model of **otitis media**, suggesting the potential usefulness of these proteins as NTHI **vaccine** components. Identification of surface-accessible B-cell epitopes could be important to efforts to develop recombinant or synthetic peptide **vaccines** based upon these **high-**

molecular-weight proteins. Thus, the purpose of the present study was to identify surface-accessible epitopes on the **HMW1** and **HMW2** proteins by using monoclonal antibodies (MAbs) and to determine the prevalence of these epitopes among the **high-molecular-weight** proteins expressed by heterologous nontypeable Haemophilus strains. MAbs were generated by **immunizing** mice with **high-molecular-weight** proteins purified from prototype strains and were screened by immunoelectron microscopy (IEM) for the ability to recognize surface epitopes. Two MAbs, designated AD6 and 10C5, that recognized surface epitopes by IEM were recovered. In order to map the epitopes recognized by these two MAbs, we constructed a set of **HMW1** and **HMW2** recombinant fusion proteins using the pGEMEX vectors and examined the reactivity of the MAbs with these fusion proteins. MAb AD6 recognized an epitope in both **HMW1** and **HMW2** which mapped to the last 75 amino acids at the carboxy termini of the two proteins. When examined for reactivity with heterologous strains, MAb AD6 recognized **high-molecular-weight** proteins in 75% of 125 unrelated nontypeable Haemophilus strains and, in addition, reacted with three of three such strains when examined by IEM. MAb 10C5 recognized an epitope that mapped to a 155-amino-acid segment near the carboxy terminus of **HMW1**. This epitope was adjacent to but distinct from the AD6 epitope and was absent from **HMW2**. The 10C5 epitope was expressed by 40% of the AD6 reactive strains. Identification of shared surface-exposed epitopes on the **high-molecular-weight** adhesion proteins suggests the possibility of developing recombinant or synthetic peptide-based **vaccines** protective against disease caused by the majority of NTHI strains.

L17 ANSWER 11 OF 28 MEDLINE
ACCESSION NUMBER: 96178615 MEDLINE
DOCUMENT NUMBER: 96178615 PubMed ID: 8606086
TITLE: **Immunization** with **high-molecular-weight** adhesion proteins of nontypeable **Haemophilus influenzae** modifies experimental **otitis media** in chinchillas.
AUTHOR: Barenkamp S J
CORPORATE SOURCE: Department of Pediatrics, St. Louis University School of Medicine, Missouri, USA.
CONTRACT NUMBER: AI-21707 (NIAID)
SOURCE: INFECTION AND IMMUNITY, (1996 Apr) 64 (4) 1246-51. Journal code: GO7; 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199605
ENTRY DATE: Entered STN: 19960531
Last Updated on STN: 19960531
Entered Medline: 19960523

AB Prevention of nontypeable **Haemophilus influenzae** **otitis media** by **vaccination** is an important health care goal. Proteins important in bacterial adherence deserve consideration as potential **vaccine**

candidates. Two colleagues and I previously identified a family of immunogenic **high-molecular-weight** proteins important in adherence of nontypeable **H. influenzae** to human epithelial cells (J.W. St. Geme III, S. Falkow, and S.J. Barenkamp, Proc. Natl. Acad. Sci. USA, 90:2875-2879, 1993). In the work described here, I determined whether **immunization** with two such adherence proteins, **HMW1** and **HMW2**, purified from prototype nontypeable Haemophilus strain 12, would modify the course of experimental **otitis media** caused by the homologous strain. Chinchillas received three monthly subcutaneous injections with 40 microgram of an **HMW1/HMW2** protein mixture in Freud's adjuvant. One month after the last injection, animals were challenged by intrabullar inoculation with 300 CFU of nontypeable **H. influenzae** 12. **Infection** developed in five of five control animals versus 5 of 10 **immunized** animals (P = 0.08, Fisher exact, one-tailed). Among **infected** animals, bacterial counts in middle ear fluid specimens 7 days postchallenge were significantly greater in control animals than in **immunized** animals (P = 0.014, Mann-Whitney U test). Serum antibody titers following **immunization** were comparable in uninfected and **infected** animals. However, **infection** in **immunized** animals was uniformly associated with the appearance of bacteria downregulated in expression of the **high-molecular-weight** proteins, suggesting bacterial selection in response to immunologic pressure. Although protection following **immunization** was incomplete, these data suggest that the **high-molecular-weight** adhesion proteins are potentially important protective **antigens** which might represent one component of a multicomponent nontypeable Haemophilus **vaccine**.

L17 ANSWER 12 OF 28 MEDLINE
ACCESSION NUMBER: 95396534 MEDLINE
DOCUMENT NUMBER: 95396534 PubMed ID: 7667057
TITLE: Acquisition of IgG serum antibodies against two Bordetella **antigens** (filamentous hemagglutinin and pertactin) in children with no symptoms of pertussis.
AUTHOR: Isacson J; Trollfors B; Taranger J; Lagergard T
CORPORATE SOURCE: Department of Pediatrics, University of Goteborg, Sweden.
SOURCE: PEDIATRIC INFECTIOUS DISEASE JOURNAL, (1995 Jun) 14 (6) 517-21.
Journal code: OXJ; 8701858. ISSN: 0891-3668.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951020
Last Updated on STN: 19970203
Entered Medline: 19951012

AB To study the specificity of serum antibodies against filamentous hemagglutinin (FHA) and pertactin for **infection** with Bordetella pertussis, we followed the acquisition of IgG serum antibodies against these 2 surface proteins of the organism in

children who had been **vaccinated** with a monocomponent pertussis toxoid **vaccine** and who had experienced no symptoms of pertussis. Antibodies were estimated with enzyme-linked immunosorbent assay. In Part 1 of our study 5 consecutive samples obtained between 3 and 36 months of age from 71 children were available. Most had maternally derived antibodies to FHA (70 of 71) and pertactin (51 of 71) in the 3-month sera which declined in the subsequent sera. From about 1 year of age there were small but significant increases in antibodies against both **antigens.** At 3 years of age 71 of 71 had antibodies to FHA and 58 of 71 had antibodies to pertactin. In Part 2 of our study sera from 109 three-year old children were available. The 12 children with a history of family exposure to pertussis had significantly higher geometric mean titers of FHA antibodies than the 97 children with no history of family exposure. The geometric mean titers of pertactin antibodies did not differ. We suggest 3 explanations for the acquisition of FHA and pertactin antibodies in children with no history of pertussis: (1) asymptomatic B. pertussis **infection** in **vaccinated** children; (2) **infection** with Bordetella parapertussis; (3) **infection** with cross-reacting **antigens** from other organisms, e.g., nonencapsulated **Haemophilus influenzae.**

L17 ANSWER 13 OF 28 MEDLINE
ACCESSION NUMBER: 92268652 MEDLINE
DOCUMENT NUMBER: 92268652 PubMed ID: 1588159
TITLE: Outer membrane proteins and lipopolysaccharides of nontypeable **Haemophilus influenzae**
AUTHOR: Barenkamp S J
CORPORATE SOURCE: Edward Mallinckrodt Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri.
CONTRACT NUMBER: AI-21707 (NIAID)
SOURCE: JOURNAL OF INFECTIOUS DISEASES, (1992 Jun) 165 Suppl 1 S181-4. Ref: 12
Journal code: IH3; 0413675. ISSN: 0022-1899.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199206
ENTRY DATE: Entered STN: 19920710
Last Updated on STN: 19920710
Entered Medline: 19920625

AB Several outer membrane proteins of nontypeable **Haemophilus influenzae** are potential **vaccine** candidates: P2 and P6 elicit antibodies that are bactericidal and protective in experimental models of **infection**. Other proteins are being investigated. A group of surface-exposed **high-molecular-weight** proteins that are major targets of antibody in human convalescent sera were identified. Monoclonal antibodies to the **high-molecular-weight** proteins of a prototype strain recognized two distinct but related proteins and were bactericidal for the prototype strain and other

strains that shared the epitope recognized by the monoclonals. Genes encoding the two proteins in the prototype strain recognized by the monoclonals were cloned and sequenced. The sequences were distinct but related, and the derived amino acid sequences had sequence similarity to that of filamentous hemagglutinin of Bordetella pertussis, an important adherence factor and protective **antigen.**

L17 ANSWER 14 OF 28 MEDLINE
ACCESSION NUMBER: 90256277 MEDLINE
DOCUMENT NUMBER: 90256277 PubMed ID: 2187812
TITLE: Expression in Escherichia coli of a **high-molecular-weight** protective surface **antigen** found in nontypeable and type b **Haemophilus influenzae.**
AUTHOR: Thomas W R; Callow M G; Dilworth R J; Audesho A A
CORPORATE SOURCE: Clinical Immunology Research Unit, Princess Margaret Hospital, Subiaco, Western Australia.
SOURCE: INFECTION AND IMMUNITY, (1990 Jun) 58 (6) 1909-13. Journal code: GO7; 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199006
ENTRY DATE: Entered STN: 19900720
Last Updated on STN: 19900720
Entered Medline: 19900625

AB An Escherichia coli clone producing a **high-molecular-weight** surface **antigen** of **Haemophilus influenzae** type b (Hib) was isolated from a library of Hib DNA fragments cloned as lysogens in a lambda replacement vector. The **antigen** is found in sarcosyl-insoluble outer membrane protein preparations and was produced by all 36 **H. influenzae** isolates tested. Absorption studies indicated that the **antigen** is a surface determinant on all isolates tested. Antibodies to the **antigen** (D15) were found in eight of nine convalescent-phase sera from children with invasive Hib **infection.** Affinity-purified antibodies prepared against the cloned **antigen** gave protection against the development of bacteremia in a rat pup model.

L17 ANSWER 15 OF 28 MEDLINE
ACCESSION NUMBER: 85078580 MEDLINE
DOCUMENT NUMBER: 85078580 PubMed ID: 2578121
TITLE: A minor **high-molecular-weight** outer membrane protein of **Haemophilus influenzae** type b is a protective **antigen.**
AUTHOR: Kimura A; Gulig P A; McCracken G H Jr; Loftus T A; Hansen E J
CONTRACT NUMBER: AI-17012 (NIAID)
AI-17621 (NIAID)
SOURCE: INFECTION AND IMMUNITY, (1985 Jan) 47 (1) 253-9. Journal code: GO7; 0246127. ISSN: 0019-9567.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198502
ENTRY DATE: Entered STN: 19900320
Last Updated on STN: 19970203
Entered Medline: 19850215

AB Cell surface-exposed antigenic determinants of several **high -molecular-weight** outer membrane proteins of **Haemophilus influenzae** type b (Hib) have been shown to be consistently immunogenic in human infants convalescing from Hib meningitis. A monoclonal antibody (mab), 6G12, directed against one of these cell surface-exposed outer membrane proteins that has an apparent molecular weight of 98,000 (98K) was identified by radioimmunoprecipitation analysis. Of 120 clinical isolates of Hib, 83 were found to possess antigenic determinants which reacted with mab 6G12 in a colony blot-radioimmunoassay procedure, indicating that the antigenic determinant recognized by mab 6G12 is present in the majority of Hib strains. A different radioimmunoassay, which uses whole Hib cells as **antigen**, confirmed that strains reactive with mab 6G12 in the colony blot-radioimmunoassay procedure possessed a cell surface-exposed and antibody-accessible antigenic determinant recognized by this mab. Hib strains which did not react with mab 6G12 were found to lack a 98K protein. Passive **immunization** with mab 6G12 reduced the level of bacteremia that developed in infant rats challenged with the homologous Hib strain against which this mab was raised. In contrast, no protection was observed when the challenge strain was one which lacks the antigenic determinant recognized by mab 6G12. Radioimmunoprecipitation analysis of sera from human infants convalescing from Hib meningitis detected an antibody response directed against the 98K protein. The protection against experimental Hib disease provided by antibody to the 98K protein, the immunogenicity of this protein in human infants, and its presence in a majority of Hib strains indicate that the 98K outer membrane protein may have potential for **vaccine** development.

L17 ANSWER 16 OF 28 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:189472 BIOSIS
DOCUMENT NUMBER: PREV200100189472
TITLE: Peptide and recombinant **antigens** for protection against bacterial middle ear **infection**.
AUTHOR(S): Bakaletz, Lauren O. (1)
CORPORATE SOURCE: (1) Department of Pediatrics, Division of Molecular Medicine, Ohio State University College of Medicine and Public Health, Children's Research Institute, 700 Children's Drive, Rm. W 302, Columbus, OH, 43205-2696: bakaletl@pediatrics.ohio-state.edu USA
SOURCE: Vaccine, (21 March, 2001) Vol. 19, No. 17-19, pp. 2323-2328. print.
ISSN: 0264-410X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Passive **immunization** of chinchillas with serum specific for either LB1 or for LPD-LB1 (f)2,1,3 prior to challenge with heterologous NTHI isolates (relative to diversity in region three of

P5-fimbrin), significantly inhibited the signs and incidence of **otitis media** (P ltoreq 0.01) induced by any of the challenge isolates. The ability of these antisera to induce total eradication of NTHI from the nasopharynx was not however equivalent among challenged cohorts. The data thus suggested that while early, complete eradication of NTHI from the nasopharynx was highly protective, reduction of the bacterial load to below a critical threshold level appeared to be similarly effective. Both immunogens thus remain strong **vaccine** candidates.

L17 ANSWER 17 OF 28 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 2001:83263 BIOSIS
DOCUMENT NUMBER: PREV200100083263
TITLE: Rapid and complete adsorption of unconjugated protein from protein-polysaccharide conjugate **vaccines.**
AUTHOR(S): Shafer, Douglas E.; Schuman, Richard F.; Lees, Andrew (1)
CORPORATE SOURCE: (1) Biosynexus Inc., 9610 Medical Center Drive, Rockville, MD, 20850: andylees@biosynexus.net USA
SOURCE: Vaccine, (8 January, 2001) Vol. 19, No. 11-12, pp. 1547-1558. print.
ISSN: 0264-410X.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB We have developed a rapid and inexpensive approach to remove unconjugated protein from protein-polysaccharide conjugate **vaccines**, without using gel filtration or ultrafiltration. We employ porous particles that adsorb the protein, whether bound or free, but with a pore size that allows only the unconjugated protein to enter the particle. Using limited amounts of media there is preferential binding of the unconjugated protein over the **high molecular weight** protein-polysaccharide conjugate. Adsorption of the unconjugated protein is rapid, with greater than 90% recovery of the conjugate. The approach is applicable to both neutral and charged polysaccharides and is not dependent on the chemistry used to make the conjugate **vaccine.** We have used this method to prepare tetanus toxoid-polysaccharide conjugates and found their immunogenicity in mice comparable to conjugates prepared using gel filtration. The method described can be used to reduce the cost and increase the yields of protein-polysaccharide conjugate **vaccines.**

L17 ANSWER 18 OF 28 BIOSIS COPYRIGHT 2001 BIOSIS
ACCESSION NUMBER: 1992:382914 BIOSIS
DOCUMENT NUMBER: BR43:49864
TITLE: A **HIGH-MOLECULAR-WEIGHT** OUTER MEMBRANE PROTEIN THAT IS A POTENTIAL TARGET FOR PROTECTIVE IMMUNITY TO TYPE B AND UNTYPABLE **HAEMOPHILUS-INFLUENZAE.**
AUTHOR(S): THOMAS W R; FLACK F S; CALLOW M G; CHUA K-Y
CORPORATE SOURCE: WEST. AUST. RES. INST. CHILD HEALTH, GPO BOX D184, PERTH 6001, WEST. AUST., AUST.
SOURCE: MEETING ON EPIDEMIOLOGY, PATHOGENESIS, AND PREVENTION OF HAEMOPHILUS INFLUENZAE DISEASE, VELDHOVEN, NETHERLANDS, SEPTEMBER 24-28, 1990. J INFECT DIS,

(1992) 165 (SUPPL 1), S75-S76.
CODEN: JIDIAQ. ISSN: 0022-1899.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L17 ANSWER 19 OF 28 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2001-272747 [28] WPIDS
DOC. NO. CPI: C2001-082667
TITLE: Conjugate **vaccine** for nontypeable **Haemophilus influenzae** comprises lipooligosaccharide from which esterified fatty acids are removed conjugated to immunogenic carrier.
DERWENT CLASS: B05
INVENTOR(S): GU, X; LIM, D J; ROBBINS, J B; TSAI, C
PATENT ASSIGNEE(S): (USSH) US DEPT HEALTH & HUMAN SERVICES
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6207157	B1	20010327	(200128)*		20

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 6207157	B1	Provisional	US 1996-16020	19960423
			US 1997-842409	19970423

PRIORITY APPLN. INFO: US 1996-16020 19960423; US 1997-842409 19970423
AN 2001-272747 [28] WPIDS
AB US 6207157 B UPAB: 20010522
NOVELTY - Conjugate **vaccine** for nontypeable **Haemophilus influenzae** comprises lipooligosaccharide from which esterified fatty acids have been removed from lipid A to form detoxified lipopolysaccharide and an immunogenic carrier covalently linked to it optionally via a linker.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(1) isolated nontypeable **Haemophilus influenzae** (NTHi) lipooligosaccharide (LOS) detoxified by removal of esterified fatty acids from lipid A to form detoxified lipooligosaccharide (dLOS) conjugated to a carrier and
(2) a pharmaceutical composition comprising the **vaccine** conjugate as above and a carrier.
ACTIVITY - Antibacterial; auditory; respiratory..
MECHANISM OF ACTION - None given.
USE - The **vaccine** is useful for prevention of **otitis media** and respiratory **infections**.
Dwg.0/5

L17 ANSWER 20 OF 28 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-618897 [59] WPIDS
DOC. NO. CPI: C2000-185397

TITLE: Novel nucleic acid encoding **Hemophilus influenzae adhesin** protein, for use as **antigens** and **vaccines** and for treating **Hemophilus influenzae infection.**

DERWENT CLASS: B04 D16

INVENTOR(S): KLEIN, M H; LOOSMORE, S M; YANG, Y

PATENT ASSIGNEE(S): (CONN-N) CONNAUGHT LAB LTD

COUNTRY COUNT: 91

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000055191	A2	20000921	(200059)*	EN	275

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000032680 A 20001004 (200101)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000055191	A2	WO 2000-CA289	20000316
AU 2000032680	A	AU 2000-32680	20000316

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000032680	A	Based on	WO 200055191

PRIORITY APPLN. INFO: US 1999-268347 19990316

AN 2000-618897 [59] WPIDS

AB WO 200055191 A UPAB: 20001117

NOVELTY - An isolated and purified nucleic acid molecule (I) comprising a sequence of 3036, 2079, 3353, 3030, 3300, 3339, 7253 or 1872 nucleotides, given in the specification, encoding a **Hemophilus influenzae adhesin** (Hia) protein comprising a sequence of 1002, 679, 1104, 1006, 1094, 1104, 2411 or 618 amino acids, given in the specification, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an isolated and purified nucleic acid molecule (Ia) encoding a N-truncated Hia protein and amplified by a nucleotide pair comprising (A), (B), (C), or (D) and (E) or (F) and (G);

(2) a vector (II) for transforming a host comprising (I) or (Ia);

(3) a host cell (III) transformed by (II) and expressing a protective Hia protein of a non-typeable strain of Hemophilus;

(4) a recombinant Hia protein produced by transformed Escherichia coli, its immunogenic fragment or functional analog;

(5) an immunogenic composition (IC) comprising (I), (Ia) or a recombinant Hia protein; and

(6) the production (P) of Hia protein.

GGGAATTCATATGGAACTCACTCTCGCACCCACACCAAATGGGCC (A)
GGGAATTCATATGACCGTGGCGGTTGCCGTATTGGCAACCCTG (B)
GGGAATTCATATGGTATTGGCAACCCTGTTGTCCGCAACG (C)
GGGAATTCATATGAATACTCCTGTTACGAATAAGTTGAAGGCT (D)
GTGTGGTAATGGAAACGCGATCGCTTTCTGGAACCACCCTAGGGC (E)
GGGAATTCATATGTCCGCAACGGTTGAGGCGAACAACAATAC (F)
TCCGGGGTTCCCCAATACGATCAATAACGAGTCGCCACCGTCGTCGC (G)

ACTIVITY - Antiinflammatory; auditory; antibacterial. No biological data is given.

MECHANISM OF ACTION - **Vaccine**. No biological data is given.

USE - An immunogenic composition (IC) comprising (I), a polypeptide (II) encoded by (I), or a recombinant HIa polypeptide (III) is useful for inducing protection against disease caused by Hemophilus strains in a susceptible host, preferably a human (claimed). The Hia protein is useful as an **antigen**, in immunogenic preparations including **vaccines**, as a carrier for other immunogens, and in the generation of diagnostic reagents. Hia is useful for treating diseases caused by the **infection** of **Hemophilus influenzae** such as meningitis, epiglottitis, septicemia and **otitis media**.

ADVANTAGE - Recombinant production of Hia favors high recovery of the protein compared to the low recovery of native protein from **Hemophilus influenzae** species. A truncated protein has a significantly higher amount of recovery than a full-length protein.

Dwg.0/32

L17 ANSWER 21 OF 28 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 2000-594517 [56] WPIDS
CROSS REFERENCE: 2000-594515 [55]; 2000-594516 [55]; 2000-679550 [64]; 2001-006956 [61]
DOC. NO. CPI: C2000-177617
TITLE: A Streptococcus pneumoniae **vaccine** for preventing pneumonia and meningitis comprises a polysaccharide **antigen** conjugated to protein D from **Haemophilus influenzae**.
DERWENT CLASS: B04 D16
INVENTOR(S): CAPIAU, C; DESCHAMPS, M; DESMONS, P M; LAFERRIERE, C A J; POOLMAN, J; PRIEELS, J
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM BIOLOGICALS
COUNTRY COUNT: 92
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000056360	A2	20000928	(200056)*	EN	77
AU 2000034307	A	20001009	(200103)		

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000056360 A2		WO 2000-EP2468	20000317
AU 2000034307 A		AU 2000-34307	20000317

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000034307 A	Based on		WO 200056360

PRIORITY APPLN. INFO: GB 1999-16677 19990715; GB 1999-6437 19990319; GB 1999-9077 19990420; GB 1999-9466 19990423

AN 2000-594517 [56] WPIDS

CR 2000-594515 [55]; 2000-594516 [55]; 2000-679550 [64]; 2001-006956 [61]

AB WO 200056360 A UPAB: 20010116

NOVELTY - A polysaccharide conjugate **antigen** (I) comprising a polysaccharide **antigen** derived from a pathogenic bacterium conjugated to protein D (or a fragment) from **Haemophilus influenzae**, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an immunogenic composition comprising (I);

(2) an immunogenic composition comprising Neisseria meningitidis protein D polysaccharide conjugate **antigen**;

(3) an immunogenic composition comprising **Haemophilus influenzae** b protein D polysaccharide conjugate **antigen**;

(4) an immunogenic composition comprising conjugated capsular polysaccharides of Streptococcus pneumoniae, **Haemophilus influenzae** b , meningococcus C and meningococcus Y, the carrier protein for at least one of the polysaccharides is protein D from **H. influenzae**;

(5) a **vaccine** comprising (1)-(4); and

(6) a method for producing an immunogenic composition to a pathogenic bacterium comprising:

(a) isolating a polysaccharide **antigen** from a pathogenic bacterium;

(b) activating the polysaccharide; and

(c) conjugating the polysaccharide to protein D.

ACTIVITY - Antibacterial. No biological data given

MECHANISM OF ACTION - **Vaccine**.

USE - The bacterial polysaccharide **antigen vaccines** are used to induce an immune response to Streptococcus pneumoniae and is used to prevent pneumonia, bacteremia, meningitis and acute **otitis media**.

ADVANTAGE - The conjugation of the **antigen** to a larger immunogenic protein increases the induced immune response, especially in children less than two years old.

Dwg.0/3

L17 ANSWER 22 OF 28 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD

ACCESSION NUMBER: 2000-303789 [26] WPIDS

DOC. NO. CPI: C2000-092308

TITLE: Nucleic acid molecule for producing recombinant

high molecular weight
proteins of Haemophilus which are used as a **vaccine** to provide protection against Haemophilus induced diseases in humans.

DERWENT CLASS: B04 D16
INVENTOR(S): KLEIN, M H; LOOSMORE, S M; YANG, Y
PATENT ASSIGNEE(S): (CONN-N) CONNAUGHT LAB LTD; (AVET) AVENTIS PASTEUR LTD
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000020609	A2	20000413	(200026)*	EN	307

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW

AU 9960736	A	20000426	(200036)	
EP 1117807	A2	20010725	(200143)	EN

R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000020609	A2	WO 1999-CA938	19991007
AU 9960736	A	AU 1999-60736	19991007
EP 1117807	A2	EP 1999-947153	19991007
		WO 1999-CA938	19991007

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9960736	A	Based on	WO 200020609
EP 1117807	A2	Based on	WO 200020609

PRIORITY APPLN. INFO: US 1998-206942 19981208; US 1998-167568 19981007
AN 2000-303789 [26] WPIDS
AB WO 200020609 A UPAB: 20000531
NOVELTY - A nucleic acid molecule (I) comprising a promoter functional in Escherichia coli and operatively coupled to a modified operon of a non-typeable strain of Haemophilus comprising A, B and C genes, where the A gene only contains a nucleic acid sequence encoding a mature **high molecular weight** protein (**HMW**) of the non-typeable strain of Haemophilus, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a vector adapted for transformation of a host comprising (I);

(2) a strain of E. coli transformed by the vector of (1) expressing a protective **HMW** protein of a non-typeable

strain of Haemophilus;

(3) a recombinant protective **HMW** protein of a non-typeable strain of Haemophilus or immunogenic fragment or analog, produced by the transformed E. coli strain of (2);

(4) a plasmid vector (II) for expression of a **HMW** protein of a non-typeable strain of Haemophilus comprising the T7 promoter, a cloning site for insertion of a nucleic acid molecule into the plasmid vector and portions B and C of the operon of a non-typeable Haemophilus strain;

(5) an isolated and purified **HMW** 1 protein of a non-typeable strain of Haemophilus free from contamination by **HMW** 2 of the same strain of non-typeable Haemophilus;

(6) an isolated and purified **HMW** 2 protein of a non-typeable strain of Haemophilus free from contamination by **HMW** 1 of the same strain of non-typeable Haemophilus;

(7) an immunogenic composition comprising at least one immunogenically-active component which is (I), the recombinant protective **HMW** protein of (3) or the **HMW** proteins of (5) or (6) and a carrier;

(8) a method for inducing protection against disease caused by Haemophilus comprising administering to a susceptible host the composition of (7); and

(9) a method for producing a protective **HMW** protein of a non-typeable strain of Haemophilus comprising transforming E. coli with the vector of (1), growing the E. coli to express the encoded mature **HMW** protein and isolating and purifying the expressed **HMW** protein.

ACTIVITY - Antibacterial.

Groups of 8-9 chinchillas were **immunized** three times intramuscularly with 30 micro g of purified rHMW1 or rHMW2, 2 x 109 colony forming units (cfu) of heat inactivated (56 deg. C for 10 minutes) **H. influenzae** (NTHi) whole cells in alum or alum alone on days 0, 14 and 28. Serum samples and nasal wash samples were taken on day 42 for measurement of anti-**HMW1** or anti-**HMW2** antibody titers by ELISAs (enzyme linked immunosorbent assays). On day 44, animals were lightly anesthetized using xylazine/ketamine hydrochloric acid by intramuscular injection. Intranasal inoculations were performed by passive inhalation (0.1 ml per animal) of freshly cultured streptomycin-resistant NTHi strain 12 in BHI (not defined) medium supplemented with hemin and nicotinamide adenine dinucleotide (NAD) both at 2 micro g ml-1. Dose of bacterial challenge was 1 x 108 cfu per animal. Nasopharyngeal lavages were performed 4 days post inoculation on chinchillas. 67-88% of control animals **immunized** with alum only had culture positive nasal lavage fluids but 67-80% of animals **immunized** with the rHMW1 protein purified from constructs abc (pDS-1046-1-1), a/abc (pBK86-1-1) or abc/cer (pBK-76-1-1) were largely protected. Animals **immunized** with constructs that did not contain intact ABC genes were 70-90% **infected**. Similar results were achieved with rHMW2 protein.

MECHANISM OF ACTION - **Vaccine**.

USE - The nucleic acids and vectors are used for the production of recombinant **H. influenzae HMW** proteins which can be used as **vaccines** to mediate a humoral or cell-mediated immune response to provide protection against **H. influenzae** induced diseases in humans.

The **HMW** proteins are also useful as **antigens** in immunoassays for detecting antibacterial, Haemophilus, **HMW** and/or peptide antibodies. The nucleotide sequences encoding the **HMW** proteins can be used to isolate and clone **hmw** genes from other non-typeable strains of Haemophilus in hybridization reactions.

ADVANTAGE - Including the cer gene of E. coli enhances the level of expression of mature **HMW** protein by the vectors.

Dwg.0/235

L17 ANSWER 23 OF 28 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1999-444322 [37] WPIDS
DOC. NO. CPI: C1999-130893
TITLE: Detoxified lipooligosaccharide-based **vaccine** for prevention of Moraxella catarrhalis **infections** in mammals.
DERWENT CLASS: B04 D16
INVENTOR(S): GU, X; ROBBINS, J B
PATENT ASSIGNEE(S): (USSH) US DEPT HEALTH & HUMAN SERVICES
COUNTRY COUNT: 85
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9936086	A1	19990722	(199937)*	EN	60
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
AU 9922212	A	19990802	(199954)		
BR 9906902	A	20001017	(200056)		
EP 1047447	A1	20001102	(200056)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
CN 1288384	A	20010321	(200137)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9936086	A1	WO 1999-US590	19990112
AU 9922212	A	AU 1999-22212	19990112
BR 9906902	A	BR 1999-6902	19990112
		WO 1999-US590	19990112
EP 1047447	A1	EP 1999-902170	19990112
		WO 1999-US590	19990112
CN 1288384	A	CN 1999-802142	19990112

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9922212	A	Based on	WO 9936086
BR 9906902	A	Based on	WO 9936086
EP 1047447	A1	Based on	WO 9936086

PRIORITY APPLN. INFO: US 1998-71483 19980113

AN 1999-444322 [37] WPIDS
AB WO 9936086 A UPAB: 19990914
NOVELTY - A lipooligosaccharide (LOS) isolated from Moraxella catarrhalis and detoxified by removal of ester-linked fatty acids to produce detoxified LOS (dLOS) or treated to remove lipid A to produce oligosaccharide (OS) is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for a conjugate **vaccine** for M. catarrhalis comprising dLOS or OS, and a covalently linked immunogenic carrier as above; methods of detoxifying LOS isolated from M. catarrhalis, by removal of ester-linked fatty acids; methods of making a conjugate **vaccine** as above.

ACTIVITY - Immunoprotective; Auditory; Antibacterial.

MECHANISM OF ACTION - **Vaccine**.

USE - The methods are useful for isolation of detoxified lipooligosaccharide or oligosaccharide from M. catarrhalis. The detoxified lipooligosaccharide or oligosaccharide are useful in conjugate **vaccines**. The **vaccine** is useful for protection against M. catarrhalis which causes **otitis media** and respiratory **infections**.

ADVANTAGE - The invention provides a detoxified lipooligosaccharide from M. catarrhalis, the major virulence factor for pathogenesis of bacterial **infections**. When tested by the standard Limulus amebocyte lysate assay, the isolated LOS showed 2 x 104 EU/ mu g, whereas the dLOS showed 1 EU/ mu g, representing a 20000-fold reduction of toxicity.

Dwg.0/3

L17 ANSWER 24 OF 28 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1997-503038 [46] WPIDS
CROSS REFERENCE: 1993-320683 [40]
DOC. NO. CPI: C1997-159973
TITLE: **High molecular weight** proteins of non-typeable **Haemophilus influenzae** - useful for **vaccine** production.
DERWENT CLASS: B04 D16
INVENTOR(S): BARENKAMP, S J
PATENT ASSIGNEE(S): (BARE-I) BARENKAMP S J; (UYSL-N) UNIV ST LOUIS; (UNIW) UNIV WASHINGTON
COUNTRY COUNT: 77
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9736914	A1	19971009	(199746)*	EN	183
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN YU					
AU 9725873	A	19971022	(199808)		
EP 900232	A1	19990310	(199914)	EN	
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
CN 1222914	A	19990714	(199946)		
US 5977336	A	19991102	(199953)		
NZ 332322	A	20000327	(200022)		

AU 723159	B	20000817 (200044)	
MX 9808107	A1	19990701 (200061)	
JP 2001503602	W	20010321 (200122)	175

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9736914	A1		WO 1997-US4707	19970401
AU 9725873	A		AU 1997-25873	19970401
EP 900232	A1		EP 1997-917597	19970401
			WO 1997-US4707	19970401
CN 1222914	A		CN 1997-195173	19970401
US 5977336	A	Cont of	WO 1993-US2166	19930316
		CIP of	US 1994-302832	19941005
			US 1996-617697	19960401
NZ 332322	A		NZ 1997-332322	19970401
			WO 1997-US4707	19970401
AU 723159	B		AU 1997-25873	19970401
MX 9808107	A1		MX 1998-8107	19981001
JP 2001503602	W		JP 1997-535346	19970401
			WO 1997-US4707	19970401

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9725873	A	Based on	WO 9736914
EP 900232	A1	Based on	WO 9736914
US 5977336	A	CIP of	US 5603938
NZ 332322	A	Based on	WO 9736914
AU 723159	B	Previous Publ.	AU 9725873
		Based on	WO 9736914
JP 2001503602	W	Based on	WO 9736914

PRIORITY APPLN. INFO: US 1996-617697 19960401; WO 1993-US2166 19930316; US 1994-302832 19941005

AN 1997-503038 [46] WPIDS

CR 1993-320683 [40]

AB WO 9736914 A UPAB: 20010421

Novel isolated and purified nucleic acids encode **high-molecular-weight** (**HMW**) proteins, **HMW3** and **HMW4**, of a non-typeable Haemophilus strain, or a variant or fragment of the protein retaining the immunological activity to protect against disease caused by a non-typeable Haemophilus strain, have: (a) The 4794 bp DNA sequence, encoding **HMW3** with the 1599 amino acid sequence; (b) the 4803 bp DNA sequence, encoding **HMW4** with the 1600 amino acid sequence; or (c) a DNA sequence encoding a **HMW** of a non-typeable Haemophilus strain, which hybridises under stringent conditions to the DNA of (a) or (b); all sequences are given in the specification.

USE - The proteins, conjugates and peptides can be used in **vaccines** against non-typeable **Haemophilus influenzae infection**. The proteins can also be used as immunogens for the preparation of antibodies, and as **antigens** for the detection of these antibodies. (I) can be used as a probe for genes for **HMW** proteins from other

strains of non-typeable **Haemophilus influenzae,**
and from any other strain of non-typeable Haemophilus.
Dwg.0/23

L17 ANSWER 25 OF 28 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1993-320683 [40] WPIDS
CROSS REFERENCE: 1994-316665 [39]; 1997-503038 [46]
DOC. NO. CPI: C1993-142729
TITLE: **High molecular weight**
surface proteins - of non-typeable haemophilus which exhibit immunogenic properties.
DERWENT CLASS: B04 D16
INVENTOR(S): BARENKAMP, S J; ST GEME, J W
PATENT ASSIGNEE(S): (UYSL-N) UNIV ST LOUIS; (UNIW) UNIV WASHINGTON; (BARE-I) BARENKAMP S J; (INRM) INSERM INST NAT SANTE & RECH MEDICALE
COUNTRY COUNT: 27
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9319090	A1	19930930	(199340)*	EN	96
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE					
W: AU BR CA FI JP KR NO RU UA US					
AU 9339168	A	19931021	(199407)		
NO 9403431	A	19941110	(199505)		
EP 632814	A1	19950111	(199506)	EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
FI 9404273	A	19941115	(199506)		
JP 07506248	W	19950713	(199536)		29
AU 669360	B	19960606	(199630)		
US 5549897	A	19960827	(199640)		100
EP 632814	A4	19960313	(199642)		
US 5603938	A	19970218	(199713)		100
BR 9306109	A	19971118	(199802)		
JP 2810235	B2	19981015	(199846)		115
US 5876733	A	19990302	(199916)		
US 5928651	A	19990727	(199936)#		
RU 2157816	C2	20001020	(200105)		
KR 219126	B1	19991001	(200108)		
US 6218141	B1	20010417	(200123)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9319090	A1	WO 1993-US2166	19930316
AU 9339168	A	AU 1993-39168	19930316
NO 9403431	A	WO 1993-US2166	19930316
		NO 1994-3431	19940915
EP 632814	A1	EP 1993-908295	19930316
		WO 1993-US2166	19930316
FI 9404273	A	WO 1993-US2166	19930316
		FI 1994-4273	19940915
JP 07506248	W	JP 1993-516604	19930316
		WO 1993-US2166	19930316
AU 669360	B	AU 1993-39168	19930316
US 5549897	A	US 1993-38682	19930316

EP 632814	A4		EP 1993-908295	
US 5603938	A		WO 1993-US2166	19930316
			US 1994-302832	19941005
BR 9306109	A		BR 1993-6109	19930316
			WO 1993-US2166	19930316
JP 2810235	B2		JP 1993-516604	19930316
			WO 1993-US2166	19930316
US 5876733	A	Cont of	WO 1993-US2166	19930316
		Cont of	US 1994-302832	19941005
			US 1995-469880	19950606
US 5928651	A	Cont of	WO 1993-US2166	19930316
		Cont of	US 1994-302832	19941005
			US 1996-728470	19961010
RU 2157816	C2		WO 1993-US2166	19930316
			RU 1994-42726	19930316
KR 219126	B1		WO 1993-US2166	19930316
			KR 1994-703224	19940915
US 6218141	B1	Div ex	WO 1993-US2166	19930316
		Div ex	US 1994-302832	19941005
			US 1996-719641	19960925

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9339168	A	Based on	WO 9319090
EP 632814	A1	Based on	WO 9319090
JP 07506248	W	Based on	WO 9319090
AU 669360	B	Previous Publ.	AU 9339168
		Based on	WO 9319090
US 5603938	A	Based on	WO 9319090
BR 9306109	A	Based on	WO 9319090
JP 2810235	B2	Previous Publ.	JP 07506248
		Based on	WO 9319090
US 5876733	A	Cont of	US 5603938
RU 2157816	C2	Based on	WO 9319090
US 6218141	B1	Div ex	US 5603938

PRIORITY APPLN. INFO: GB 1992-5704 19920316; US 1996-728470 19961010

AN 1993-320683 [40] WPIDS

CR 1994-316665 [39]; 1997-503038 [46]

AB WO 9319090 A UPAB: 20010603

An isolated and purified gene exceeding a **high mol . wt.** (HMV) protein (I) of a non-tyeable Haemophilis strain (HP).

Also claimed are: (A) a purified and isolated gene cluster comprising a nucleotide sequence (NS) for a structural gene encoding (I) of a non-typeable HP; and more than 1 downstream NS for on accessory gene for affecting expression of a gene product fully enclosed by the structural gene. (B) (I) of non-typeable HP encoded by a gene as above, or its variant or fragment retaining the immunological ability to protect against disease caused by a non-typeable HP; (C) on isolated and purified (I) of non-typeable HV filaments haemoglutinin surface protein of Bordetella pertussis, (D) a conjugate comprising (I) linked to anantigen, hapten or polysaccharide for elicting on immune response to the **antigen**, hapten or polysaccharide; and (E) a synthetic

peptide having on aminoacid sequence corresponding to more than 1 protective epitope of a **HMW** protein of non-typeable **H. influenzae.**

ADVANTAGE - With the isolation of and purification of (I), it is possible to determine the major protective epitopes by conventional epitope mapping and synthesise peptide corresponding to these determinants to be incorporated in fully synthetic or recombinant **vaccines**

Dwg.0/10

ABEQ US 5549897 A UPAB: 19961007

A **vaccine** against disease caused by non-typeable **Haemophilus influenzae**, including **otitis media**, sinusitis and bronchitis, comprising an effective amount of a **high molecular weight** protein of non-typeable **Haemophilus influenzae** which is protein **HMW1** and/or **HMW2** and a physiological carrier therefor.

Dwg.0/10

ABEQ US 5603938 A UPAB: 19970326

A 1536 amino acid (sequence given in the specification) **high molecular weight** non-typeable **Haemophilus influenzae** surface protein and a 5116 base pair DNA sequence (also given in the specification) are new.

Dwg.0/10

L17 ANSWER 26 OF 28 SCISEARCH COPYRIGHT 2001 ISI (R)

ACCESSION NUMBER: 2000:656776 SCISEARCH

THE GENUINE ARTICLE: 346KM

TITLE: Enhancement of clearance of bacteria from murine lungs by **immunization** with detoxified lipooligosaccharide from Moraxella catarrhalis conjugated to proteins

AUTHOR: Hu E G; Chen J; Battey J F; Gu X X (Reprint)

CORPORATE SOURCE: NIDCD, IMMUNOL LAB, NIH, 5 RES COURT, 2A31, ROCKVILLE, MD 20850 (Reprint); NIDCD, IMMUNOL LAB, NIH, ROCKVILLE, MD 20850

COUNTRY OF AUTHOR: USA

SOURCE: INFECTION AND IMMUNITY, (SEP 2000) Vol. 68, No. 9, pp. 4980-4985.
Publisher: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904.
ISSN: 0019-9567.

DOCUMENT TYPE: Article; Journal

FILE SEGMENT: LIFE

LANGUAGE: English

REFERENCE COUNT: 45

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Moraxella catarrhalis strain 25238 detoxified lipooligosaccharide (dLOS)-protein conjugates induced a significant rise of bactericidal anti-LOS antibodies in animals. This study reports the effect of active or passive **immunization** with the conjugates or their antiserum on pulmonary clearance of M. catarrhalis in an aerosol challenge mouse model. Mice were injected subcutaneously with dLOS-tetanus toxoid (dLOS-TT), dLOS-**high-molecular-weight** proteins (dLOS-HMP) from nontypeable **Haemophilus influenzae** (NTHi), or nonconjugated materials in Ribi adjuvant and then challenged with M. catarrhalis strain 2-5238 or O35E or NTHi strain 12.

Immunization with dLOS-TT or dLOS-HMP generated a significant rise of serum anti-LOS immunoglobulin G and 68% and 35 to 41% reductions of bacteria in lungs compared with the control ($P < 0.01$) following challenge with homologous strain 25238 and heterologous strain O35E, respectively. Serum anti-LOS antibody levels correlated with its bactericidal titers against M. catarrhalis and bacterial CFU in lungs. Additionally, **immunization** with dLOS-HMP generated a 54% reduction of NTHi strain 12 compared with the control ($P < 0.01$). Passive **immunization** with a rabbit antiserum against dLOS-TT conferred a significant reduction of strain 25238 CFU in lungs in a dose- and time-dependent pattern compared with preimmune serum-treated mice. Kinetic examination of lung tissue sections demonstrated that antiserum-treated mice initiated and offset inflammatory responses more rapidly than preimmune serum-treated mice. These data indicate that LOS antibodies (whether active or passive) play a major role in the enhancement of pulmonary clearance of different test strains of M. catarrhalis in mice. In addition, dLOS-HMP is a potential candidate for a bivalent **vaccine** against M. catarrhalis and NTHi **infections**.

L17 ANSWER 27 OF 28 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 2000:155970 SCISEARCH
THE GENUINE ARTICLE: 285UW
TITLE: Immune responses to specific **antigens** of Streptococcus pneumoniae and Moraxella catarrhalis in the respiratory tract
AUTHOR: Samukawa T; Yamanaka N; Hollingshead S; Klingman K; Faden H (Reprint)
CORPORATE SOURCE: CHILDRENS HOSP BUFFALO, DIV INFECT DIS, 219 BRYANT ST, BUFFALO, NY 14222 (Reprint); WAKAYAMA MED COLL, WAKAYAMA 640, JAPAN; UNIV ALABAMA, BIRMINGHAM, AL; SUNY BUFFALO, SCH MED & BIOMED SCI, BUFFALO, NY 14260
COUNTRY OF AUTHOR: USA; JAPAN
SOURCE: INFECTION AND IMMUNITY, (MAR 2000) Vol. 68, No. 3, pp. 1569-1573.
Publisher: AMER SOC MICROBIOLOGY, 1325 MASSACHUSETTS AVENUE, NW, WASHINGTON, DC 20005-4171.
ISSN: 0019-9567.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 28

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Streptococcus pneumoniae and Moraxella catarrhalis are two common respiratory pathogens, colonizing as many as 54 and 72% of children, respectively, by 1 year of age. The immune responses to surface protein A of S. pneumoniae (PspA) and the **high-molecular-weight** outer membrane protein of M. catarrhalis (UspA) in the sera of various age groups in the general population and in the nasopharynges of 30 children monitored from birth through 1 year of age were evaluated. Immunoglobulin G (IgG) was the dominant serum antibody to PspA and UspA. Whereas the serum antibody response to PspA peaked in childhood, the antibody response to UspA peaked in adulthood. In the first 2 years of life, comparable amounts of IgM and IgG antibodies to both proteins were observed. In older persons, IgG antibodies to both **antigens**

predominated over IgM antibodies. The levels of IgA antibody to these **antigens** in serum remained low during the first 2 years of life. The levels of IgM antibody to the two **antigens** in serum exceeded the levels of IgA antibody to the same two **antigens** throughout life. Although IgA was the dominant antibody to PspA and UspA in airway secretions, it was detected in a minority of the children (3 of 15 for PspA and 0 of 15 for UspA). Even the majority of the children previously colonized with these pathogens lacked antibody to them in their secretions.

L17 ANSWER 28 OF 28 SCISEARCH COPYRIGHT 2001 ISI (R)
ACCESSION NUMBER: 1998:98321 SCISEARCH
THE GENUINE ARTICLE: YT330
TITLE: Outer-membrane **antigen** expression by Moraxella (Branhamella) catarrhalis influences pulmonary clearance
AUTHOR: Kyd J M; Cripps A W; Murphy T F (Reprint)
CORPORATE SOURCE: UNIV CANBERRA, FAC SCI APPL, BELCONNEN, ACT 2616, AUSTRALIA (Reprint); UNIV CANBERRA, FAC SCI APPL, BELCONNEN, ACT 2616, AUSTRALIA; SUNY BUFFALO, DEPT MED, DIV INFECT DIS, BUFFALO, NY 14260; SUNY BUFFALO, DEPT MICROBIOL, BUFFALO, NY 14260
COUNTRY OF AUTHOR: AUSTRALIA; USA
SOURCE: JOURNAL OF MEDICAL MICROBIOLOGY, (FEB 1998) Vol. 47, No. 2, pp. 159-168.
Publisher: CHAPMAN HALL LTD, 2-6 BOUNDARY ROW, LONDON, ENGLAND SE1 8HN.
ISSN: 0022-2615.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 21

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Moraxella (Branhamella) catarrhalis is a common respiratory tract pathogen in man. The bacterium shows a strong tendency to form aggregates in vitro. A variant strain of M. catarrhalis that showed a reduced tendency to form aggregates was selected by successive in-vitro passage in broth culture from which aggregates had settled. The non-clumping variant strain showed alteration in expression of outer-membrane **antigens**, including the **HMW**-OMP, an outer-membrane protein of c. 200 kDa, outer-membrane protein CD and lipo-oligosaccharide. A mouse model for pulmonary challenge with M. catarrhalis revealed significant differences in the rate of clearance of the isogenic variant strains from the lung. The parent strain caused enhanced recruitment of neutrophils to the lung and more rapid clearance of bacteria from the lungs in comparison to the non-clumping variant. It is concluded that alteration of expression of surface molecules by M. catarrhalis has a significant impact in an in-vivo model of pulmonary clearance.

=> fil hom
FILE 'HOME' ENTERED AT 09:36:39 ON 26 OCT 2001

<------User Break------>

=> d his; d cost

(FILE 'HOME' ENTERED AT 08:57:02 ON 26 OCT 2001)

FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 15:11:37 ON 26 OCT 2001

- Author (S)

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L22          284 SEA ABB=ON  PLU=ON  LOOSMORE S?/AU
L23        26890 SEA ABB=ON  PLU=ON  YANG Y?/AU
L24        12603 SEA ABB=ON  PLU=ON  KLEIN M?/AU
L25          104 SEA ABB=ON  PLU=ON  L22 AND L23 AND L24
L26          215 SEA ABB=ON  PLU=ON  L22 AND (L23 OR L24)
L27          150 SEA ABB=ON  PLU=ON  L23 AND L24
L28        39412 SEA ABB=ON  PLU=ON  L22 OR L23 OR L24
L29          214 SEA ABB=ON  PLU=ON  (L25 OR L26 OR L27 OR L28) AND
                 INFLUENZAE
L30           76 SEA ABB=ON  PLU=ON  L29 AND ANTIGEN
L31           38 DUP REM L30 (38 DUPLICATES REMOVED)

     FILE 'REGISTRY' ENTERED AT 15:14:22 ON 26 OCT 2001
L32          239 SEA ABB=ON  PLU=ON  ADHESIN ?/CN

     FILE 'CAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH,
     JICST-EPLUS, JAPIO' ENTERED AT 15:14:36 ON 26 OCT 2001
L33            7 SEA ABB=ON  PLU=ON  L31 AND (L32 OR ADHESIN OR HMW# OR
                 (HIGH OR HI)(W)(MOL OR MOLECUL?)(W)(WT OR WEIGHT))
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L33 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:63846 CAPLUS
DOCUMENT NUMBER: 134:120915
TITLE: Multicomponent vaccine to protect against disease caused by Haemophilus **influenzae** and Moraxella catarrhalis
INVENTOR(S): **Loosmore, Sheena M.; Yang, Yan-Ping; Klein, Michel H.;** Sasaki, Ken
PATENT ASSIGNEE(S): Connaught Laboratories Limited, Can.
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001005424	A2	20010125	WO 2000-CA811	20000711
WO 2001005424	A3	20010802		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-353617 A 19990715

AB A multi-valent immunogenic compn. confers protection on an immunized host against infection caused by both Haemophilus **influenzae** and Moraxella catarrhalis. Such compn. comprises at least four **antigens** comprising at least one **antigen** from

Haemophilus **influenzae**, and at least one **antigen** from Moraxella catarrhalis. Three of the **antigens** are **adhesins**. **High mol. wt.** (**HMW**) proteins and Haemophilus **influenzae** **adhesin** (Hia) proteins of non-typeable Haemophilus and a 200 kDa outer membrane protein of Moraxella catarrhalis comprise the **adhesin** components while the other **antigen** is a non-proteolytic analog of Hin47 protein. Each component does not impair the immunogenicity of the others. The multi-valent immunogenic compn. may be combined with DTP component vaccines, which may also include non-virulent poliovirus and PRP-T, to provide a component vaccine without impairment of the immunogenic properties of the other **antigens**.

L33 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:666762 CAPLUS
DOCUMENT NUMBER: 133:263796
TITLE: **Adhesins** of non-typable Haemophilus **influenzae** and their manufacture for vaccine use
INVENTOR(S): **Loosmore, Sheena M.; Yang, Yan-Ping; Klein, Michel H.**
PATENT ASSIGNEE(S): Connaught Laboratories Limited, Can.
SOURCE: PCT Int. Appl., 275 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000055191	A2	20000921	WO 2000-CA289	20000316
WO 2000055191	A3	20010802		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-268347 A2 19990316

AB Cloning and expression of the Hia gene of non-typeable strains of Haemophilus **influenzae** is described for manuf. of the proteins for use in vaccines. The nucleic acid and deduced amino acid sequences of Hia genes of various strains of non-typeable and type c Haemophilus **influenzae** also are described. Use of full-length and truncated forms of the protein to induce protective immunity to H. **influenzae** is demonstrated. Antibody from immunized guinea pigs gave passive immunity to infant rats.

L33 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:628017 CAPLUS
DOCUMENT NUMBER: 133:221585
TITLE: Multi-component vaccine against non-typeable Haemophilus **influenzae**

INVENTOR(S): **Loosmore, Sheena M.; Yang, Yan-Ping; Klein, Michel H.**
PATENT ASSIGNEE(S): Connaught Laboratories Limited, Can.
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000051633	A2	20000908	WO 2000-CA207	20000229
WO 2000051633	A3	20010125		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-261182 A 19990303

AB The authors disclose a vaccine compn. comprising at least three different **antigens** of Haemophilus **influenzae**, two of which are **adhesins**. **High mol. wt.** (**HMW**) proteins and Haemophilus **influenzae adhesin** (Hia) proteins comprise the **adhesin** components while the other **antigen** is a non-proteolytic analog of Hin47 protein. Each component does not impair the immunogenicity of the others. The multi-component vaccine afforded protection against otitis media in a chinchilla nasopharyngeal colonization model and partial protection in intrabulla challenge. The Haemophilus vaccine may be combined with DTP vaccine components to provide a multi-valent vaccine without impairment of the immunogenic properties of the other **antigens**.

L33 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:420981 CAPLUS
DOCUMENT NUMBER: 133:57570
TITLE: Multi-component vaccine comprising at least two **antigens** from Haemophilus **influenzae** to protect against disease
INVENTOR(S): **Loosmore, Sheena M.; Yang, Yan-ping; Klein, Michel H.**
PATENT ASSIGNEE(S): Connaught Laboratories Ltd., Can.
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000035477	A2	20000622	WO 1999-CA1189	19991215

WO 2000035477 A3 20001026
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
EP 1140158 A2 20011010 EP 1999-957822 19991215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
PRIORITY APPLN. INFO.: US 1998-210995 A 19981215
WO 1999-CA1189 W 19991215

AB A multi-component immunogenic compn. confers protection on an immunized host against infection caused by Haemophilus **influenzae** . Such compn. comprises at least two different **antigens** of Haemophilus **influenzae** , one of which is an **adhesin. High mol. wt** . (**HMW**) proteins of non-typeable Haemophilus **influenzae** enhance the immune response in a host to a non-proteolytic analog of Hin47 protein in such immunogenic compns. with one component not impairing the immunogenicity of the other. The Haemophilus vaccine may be combined with DTP component vaccines to provide a multi-valent component vaccine without impairment of the immunogenic properties of the other **antigens.**

L33 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:241525 CAPLUS
DOCUMENT NUMBER: 132:292707
TITLE: **High molecular weight** proteins **HMW1** and **HMW2** as protective **antigens** against non-typable Haemophilus **influenzae** infection
INVENTOR(S): **Loosmore, Sheena M.; Yang, Yan-ping; Klein, Michel H.**
PATENT ASSIGNEE(S): Connaught Laboratories Limited, Can.
SOURCE: PCT Int. Appl., 307 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000020609	A2	20000413	WO 1999-CA938	19991007
WO 2000020609	A3	20000803		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF,

BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
AU 9960736 A1 20000426 AU 1999-60736 19991007
EP 1117807 A2 20010725 EP 1999-947153 19991007
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
PRIORITY APPLN. INFO.: US 1998-167568 A2 19981007
US 1998-206942 A 19981208
WO 1999-CA938 W 19991007

AB **High mol. wt.** (**HMW**) proteins for use as protective **antigens** against infection by non-typable Haemophilus **influenzae** infection are manufd. by expression of the cloned genes in Escherichia coli. The proteins are manufd. using a modified **HMW** operon that contains only the portion of the A region that encodes the mature **HMW** protein and the complete B and C regions of the operon. Increased levels of synthesis of the **HMW** proteins can be achieved by including the E. coli cer gene, a further copy of the portion of the A region of the operon encoding the mature protein or both, in the expression vector. Nucleotide and deduced amino acid sequences of the **hmw1** and **hmw2** genes and **HMW1** and **HMW2** proteins, resp., of several non-typeable Haemophilus **influenzae** strain have been identified. The construction of expression vectors, manuf. and purifn. of the proteins and testing of their protective effects in chinchillas are demonstrated.

L33 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:296924 CAPLUS
DOCUMENT NUMBER: 129:39889
TITLE: Nasopharyngeal colonization with nontypeable Haemophilus **influenzae** in chinchillas
AUTHOR(S): **Yang, Yan-Ping; Loosmore, Sheena M.**; Underdown, Brian J.; **Klein, Michel H.**
CORPORATE SOURCE: Research Center, Pasteur Merieux Connaught Canada, North York, ON, M2R 3T4, Can.
SOURCE: Infect. Immun. (1998), 66(5), 1973-1980
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Colonization of the nasopharynx by a middle ear pathogen is the first step in the development of otitis media in humans. The establishment of an animal model of nasopharyngeal colonization would therefore be of great utility in assessing the potential protective ability of candidate vaccine **antigens** (esp. **adhesins**) against otitis media. A chinchilla nasopharyngeal colonization model for nontypeable Haemophilus **influenzae** (NTHI) was developed with antibiotic-resistant strains. This model does not require coinfection with a virus. There was no significant difference in the efficiency of NTHI colonization between adult (1- to 2-yr-old) and young (2- to 3-mo-old) animals. However, the incidence of middle ear infection following nasopharyngeal colonization was significantly higher in young animals (83 to 89%) than in adult chinchillas (10 to 30%). Chinchillas that had recovered either from a previous middle ear infection caused by NTHI or from an infection by intranasal inoculation with NTHI were completely protected against nasopharyngeal colonization with a homologous strain and were the best pos. controls in protection

studies. Systemic immunization of chinchillas with inactivated whole-cell prepns. significantly protected animals not only against homologous NTHI colonization but also partially against heterologous NTHI infection. In all protected animals, significant serum anti-P6 and anti-**HMW** antibody responses were obsd. The outer membrane P6 and **high-mol.-wt.** (**HMW**) proteins appear to be promising candidate vaccine **antigens** to prevent nasopharyngeal colonization and middle ear infection caused by NTHI.

L33 ANSWER 7 OF 7 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
ACCESSION NUMBER: 1996-425088 [42] WPIDS
DOC. NO. CPI: C1996-133879
TITLE: Recombinant constructs for expressing and opt. secreting proteins in Bordetella - comprise Bordetella promoter coupled to non-Bordetella, esp. cholera B toxin, gene or coupled to non-Bordetella leader and gene of interest.
DERWENT CLASS: B04 D16
INVENTOR(S): **KLEIN, M H; LOOSMORE, S M;** YACOOB, R K; ZEALEY, G R
PATENT ASSIGNEE(S): (CONN-N) CONNAUGHT LAB LTD
COUNTRY COUNT: 71
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9626282	A1	19960829	(199642)*	EN	61
RW: AT BE CH DE DK EA ES FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG					
W: AL AM AT AU AZ BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE HU IS JP KE KG KP KR KZ LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG US UZ VN					
AU 9647100	A	19960911	(199651)		
EP 813603	A1	19971229	(199805)	EN	
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
US 5932714	A	19990803	(199937)		
US 5942418	A	19990824	(199941)		
US 5998168	A	19991207	(200004)#		
US 6140082	A	20001031	(200057)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9626282	A1		WO 1996-CA107	19960223
AU 9647100	A		AU 1996-47100	19960223
EP 813603	A1		EP 1996-902830	19960223
			WO 1996-CA107	19960223
US 5932714	A	Cont of	US 1995-393334	19950223
			US 1995-472171	19950607
US 5942418	A	CIP of	US 1995-393334	19950223
			WO 1996-CA107	19960223
			US 1997-894526	19971201
US 5998168	A	Cont of	US 1995-472171	19950607
			US 1998-13047	19980126
US 6140082	A	Cont of	US 1995-393334	19950223
			US 1999-374597	19990816

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9647100	A	Based on	WO 9626282
EP 813603	A1	Based on	WO 9626282
US 5942418	A	Based on	WO 9626282
US 5998168	A	Cont of	US 5932714

PRIORITY APPLN. INFO: US 1995-393334 19950223; US 1995-472171 19950607; US 1997-894526 19971201; US 1998-13047 19980126; US 1999-374597 19990816

AN 1996-425088 [42] WPIDS

AB WO 9626282 A UPAB: 19961021

Novel nucleic acid comprises a promoter functional in Bordetella and either (i) operatively coupled to a heterologous gene encoding a non-Bordetella gene prod., or (ii) coupled to a sequence coding for a non-Bordetella leader for secretion of a gene prod.(which may be a Bordetella or a non-Bordetella gene prod.).

Also claimed are: (1) a plasmid adapted for transformation of a Bordetella strain comprising a nucleic acid molecule which comprises a first DNA sequence corresp. to a 5'- flanking sequence of the Bordetella gene at its 5'- end, and a second DNA sequence corresp. to a 3'-flanking sequence of the Bordetella gene at its 3'-end, where these DNAs allow specific integration of the nucleic acid into a Bordetella genome at a locus corresp. to the Bordetella gene; (2) a recombinant Bordetella strain contg. the nucleic acid, opt. with a leader sequence and secreting the gene prod., or which is integrated into its genome as in (1) and which secretes the gene prod.; and (3) a nucleic acid with a sequence of 312 nucleotides given in the specification, i.e. a synthetic cholera toxin B subunit gene (designated ctb) based on Vibrio cholerae strain 569B.

USE - The transformed Bordetella strains can be used to express gene prods. such as enzymes, **antigens** (e.g. the **high mol. wt.** outer membrane protein **HMW1** or **HMW2** of a non-typable Haemophilus **influenzae** strain), immunogens, allergens, enzyme inhibitors, hormones, lymphokines, immunoglobulins (or their fragments), toxins, mammalian proteins, structural proteins or receptors. Esp. the Bordetella strains are engineered to produce a cholera toxin B subunit.

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